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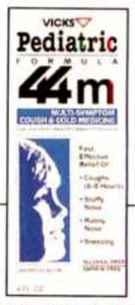

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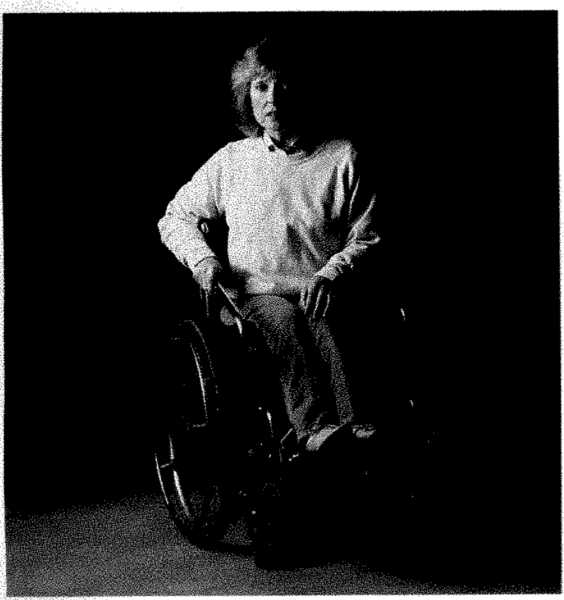

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WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any febrile illness or acute infection and in those with any advanced debilitated condition or persistent vomiting or diarrhea, or suspected gastroenteritis infection.

Other viruses (including poliovirus and other enteroviruses) may compromise the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis. **Records Required by the National Childhood Vaccine Injury Act:** Manufacturer and lot number of vaccine administered must be recorded by health care provider in vaccine recipient's permanent record, along with date of administration and name, address, and title of person administering vaccine.

Health care provider must report to a health department or to the FDA the occurrence following immunization of any event set forth in the Vaccine Injury Table including: paralytic poliomyelitis — in a nonimmunodeficient recipient within 30 days of vaccination — in an immunodeficient recipient within 6 months of vaccination; any vaccine-associated community case of paralytic poliomyelitis; or any acute complication or sequela (including death) of above events.

Use in Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with Poliovirus Vaccine Live Oral Trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. A large retrospective study suggests that OPV may be temporally associated with Guillain-Barré syndrome. A causal relationship has not been established. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts.

The Centers for Disease Control report that during the years 1973 through 1984 approximately 274.1 million OPV doses were distributed in the US. During this same period, 105 vaccine-associated cases were reported (1 case per 2.6 million doses distributed). Of these 105 cases, 35 occurred in vaccine recipients (1 case per 7.8 million doses distributed), 50 occurred in household and nonhousehold contacts of vaccinees (1 case per 5.5 million doses distributed), 14 occurred in immunodeficient recipients or contacts, and 6 occurred in persons with no history of vaccine exposure, from whom vaccine-like viruses were isolated.

Thirty-three (94%) of the recipient cases, 41 (82%) of the contact cases, and 5 (36%) of the immune deficient cases were associated with the recipient's first dose of OPV. Because most cases of vaccine-associated paralysis have occurred in association with the first dose, the CDC has estimated the likelihood of paralysis in association with first v subsequent doses of OPV, using the number of births during 1973-1984 to estimate the number of first doses distributed, and subtracting this from the total distribution to estimate the number of subsequent doses distributed. This method estimates a frequency of paralysis for recipients of 1 case per 1.2 million first doses v one case per 116.5 million subsequent doses; for contacts, one case per 1 million first doses v one case per 25.9 million subsequent doses; with an overall frequency of 1 case per 520,000 first doses v 1 case per 12.3 million subsequent doses.

Other methods of estimating the likelihood of paralysis in association with OPV have been described. Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults 2 doses of enhanced potency IPV a month apart before the children receive ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the second dose of enhanced potency IPV. A booster dose of enhanced potency IPV can be given to partially immunized adults at the same visit that the first dose of OPV is given to the child. The adult should be informed of precautions, such as handwashing after changing diapers.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults… [with IPV]… before giving OPV to the child."

The American Academy of Pediatrics and the American College of Physicians have made similar recommendations.

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8. Each table should be typed, with a title, on a separate sheet of paper, with each line, including headings, *double-spaced.* Continuations should be on a second sheet with all headings repeated.
9. Use Système International (SI) measurements throughout the manuscript.
10. Illustrations should be high-contrast, glossy prints, in quadruplicate, in a proportion of 5x7 in. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed *label* and affixed on the back of each illustration. *Do not write directly on the print.*

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11. References should be listed in order of their appearance in the text, typed double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below. Note: List all authors and/or editors up to six; if more than six, list the first three and "et al."

Journal articles: Bier DM, Fulginiti VA, Garfunkel JM, et al. Duplicate publication and related problems. *AJDC.* 1990;144:1293-1294.

Books: Naeye RL. How and when does antenatal hypoxia damage fetal brains? In: Kubli F, Patel N, Schmidt W, Linderkamp O, eds. *Perinatal Events and Brain Damage in Surviving Children.* New York, NY: Springer Verlag NY Inc; 1988:83-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

Authors are responsible for the accuracy of the references.

12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.
13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from *publisher* and *author.* Brief acknowledgments to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references.

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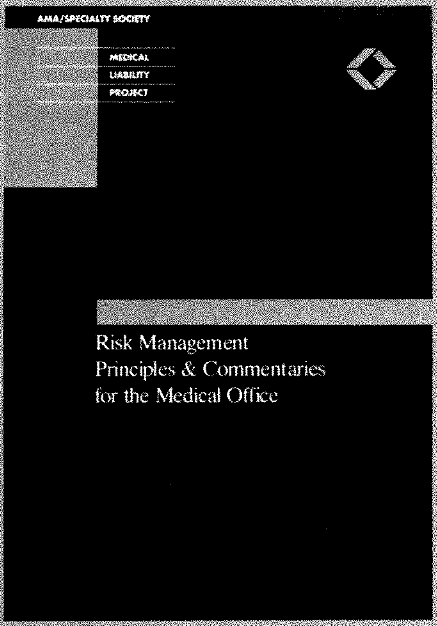

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The 1992 General Pediatrics Certifying Examination will be administered Tuesday and Wednesday, October 27 & 28, 1992, in various cities throughout the United States and Canada. For new applicants, regular registration begins December 2, 1991, and continues through March 2, 1992. The registration fee is $1050. The registration fee must accompany the completed application material and be *postmarked* by March 2. On December 2, 1991, application material will be sent to qualified residents at their training program addresses. However, any resident who does not receive the material by mid-December should request the material directly from the American Board of Pediatrics. A three-part partial payment plan will be available for *new* applicants only. The deadline for participation in that plan is January 13; details will be included in the application material. Late registration for new applicants begins March 3. The late registration fee is $1250, which includes a $200 nonrefundable late fee. The final deadline for receipt of applications from new applicants is May 1. In mid-February, reregistration material will be mailed to active candidates who meet the examination requirements. Those who do not meet the examination requirement of having a copy of their permanent, unrestricted license on file will not be sent the reregistration material. Regular reregistration begins February 17 and continues through April 17. Qualified individuals who do not receive the material by March 2 should request the material directly from the American Board of Pediatrics. The reregistration fee is $950. The reregistration fee must accompany the completed reregistration form and be *postmarked* by April 17. Late reregistration begins April 18. The late reregistration fee is $1150, which includes a $200 nonrefundable late fee. The final deadline for receipt of reregistration material is May 1, 1992. Site assignment is based on the date of receipt of the application or the reregistration material. Seating may be limited at some sites, so early registration is suggested. Correspondence to the American Board of Pediatrics should be sent to 111 Silver Cedar Ct, Chapel Hill, NC 27514-1651 ([919] 929-0461).

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The American Board of Pediatrics will administer the Certifying Examination in Pediatric Cardiology Tuesday, August 11, 1992, in three US cities. Applications are available now. Registration will continue through January 31, 1992. The application fee for the examination is $1150, but applications postmarked after December 31, 1991, must include an additional $200 late fee. New applications postmarked after January 31 *cannot be accepted* for the 1992 examination. Each application will be considered individually and must be acceptable to the Sub-board of Pediatric Cardiology. Please contact the American Board of Pediatrics for eligibility requirements. Reregistration materials will be mailed to eligible candidates on January 2. The reregistration fee is $1050. Please direct inquiries to the American Board of Pediatrics, 111 Silver Cedar Ct, Chapel Hill, NC 27514-1651 ([919] 929-0461).

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Importance of Family History in Adolescent Gallbladder Disease

Sir.—As medical students, we all learned the "Rule of Fs" in relation to gallbladder disease, ie, its predilection for fat, fecund, females aged 40 to 50 years with a fatty food intolerance. As an adolescent medicine specialist, I have always taught that the rules for gallbladder disease in teenagers are the same: a fat, fecund female aged 15 years with fatty food problems is most at risk, but I suggest adding an extra "F" for family history of early gallbladder disease.

For this reason I was disturbed that there was no mention of family history in the review of cases of childhood gallbladder disease in the January 1991 issue of *AJDC*.[1] I would be very interested in those data, particularly for the idiopathic cases that accounted for one fifth of the sample, and also for the pregnant teenagers.

In teenagers, it is always better, in my opinion, to look for hepatitis or the Fitzhugh-Curtis syndrome of gonorrheal/chlamydial perihepatitis in the differential diagnosis of right upper quadrant pain, with gallbladder disease being well down on the list unless the Rule of Fs applies, particularly when there is a family history of gallbladder disease before age 30 years or, of course, if metabolic disease is present.

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1. Reif S, Sloven DG, Lebenthal E. Gallstones in children: characterization by age, etiology, and outcome. *AJDC.* 1991;145:105-108.

In Reply.—Dr Goldenring has raised a legitimate point. We were aware of the association of family history in gallbladder disease; however, due to the fact that our work was based mainly on reviews of medical records, we could not draw any definitive conclusion. Although family history was not mentioned in many of the records, that does not mean that it did not exist. In only one case was there a positive family history for cholelithiasis, and that case was part of the idiopathic group. Further studies are needed to determine whether family history is more associated with cholelithiasis in children than in adults, particularly in the idiopathic group.

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God, Gays, and Health Care Provision

Sir.—I am writing with regard to a letter by Dr Fikar and Ms Koslap-Petraco published in the March 1991 issue of *AJDC.*[1] They do well to point out that gay youth have significant problems, including a high rate of suicide. They are indeed "valid and wholesome human beings." We do need to be concerned about these teenagers.

The authors are mistaken, however, in their assertion that "it is perfectly acceptable to be gay." Those of us who are Christians need to point out that God hates homosexuality. This is made clear in Leviticus 18:22, which calls homosexuality an "abomination." Even more condemnatory is the passage in I Corinthians 6:9 that declares that homosexuals will not be found in the kingdom of God. No wonder gays are depressed!

We do young people no favor by helping them to "feel good about themselves" when they are involved in homosexual behavior. Rather, we can let them know how much God loves them (and we do, too) and show them that God can change them so that they will be perfectly acceptable to Him. Then, they may confidently feel good about themselves.

Robert R. Jones, MD
900 S Adams
Nevada, MO 64772

1. Fikar CR, Koslap-Petraco M. What about gay teenagers? *AJDC.* 1991; 145:252.

In Reply.—We were quite surprised that a letter such as Dr Jones' would be printed in *AJDC*. The Pediatric Forum is a place for the rational discussion of issues of current concern and importance for children's health. All Biblical references in Dr Jones' letter were written before the birth of Christ or very shortly thereafter.

Times were very different then. Humanity was struggling with a number of issues that no longer exist. New problems have arisen, problems of perplexing difficulty, that were unknown to the very inspired but ancient people who set down the text of the Bible.

Since the writing of the passages quoted by Dr Jones, much has occurred in the history of humanity. There has been a Renaissance, a Reformation, an Industrial Revolution, an American Revolution, a Civil War, two world wars, a Civil Rights Movement, a Women's Rights Movement, and a Gay Rights Movement. All of these have been noble attempts by groups of people to improve the human condition or correct the problems or great injustices of previous generations.

Dr Jones does not seem to be drawing on these 2000 years of progress in his statement. It is also evident from his letter that he is confusing gayness, being gay, and gay sexuality. This is a journal of rationality and medicine, not a journal of religion. We respect Dr Jones' views, but we strongly reject his weak attempt to impose his personal value judgments on gay teenagers or gay people in general. We do not believe Dr Jones has the right to presume to speak for "Christians" or even for God. His signed credentials are those of a physician, not those of a rabbi, minister, deacon, priest, or other religious scholar or leader.

We believe that the concepts espoused in Dr Jones' letter are archaic and outmoded and have no place in current pediatric and adolescent medicine. We wish to reemphasize our original statement concerning the wholesomeness and validity of both gay people and gayness itself. It would be wrong, cruel, and irrational to attempt to force a person to change his or her sexual orientation. Such thoughts are so contrary to modern psychological and medical literature that we strongly question whether professional people who advocate such views are benefiting from the many continuing education programs now in existence.

We firmly believe that all individuals have a right to unconditional acceptance into the human community, and that they have the right to achieve their full potential as human persons. It is the responsibility of pediatric health care providers to assist all children and adolescents to develop, mature, and build self-esteem so that they will be able to feel good about themselves and their sexuality, regardless of their particular orientation. We are very proud of the work we do, and we smile with pride upon all our patients.

Charles R. Fikar, MD
Mary Koslap-Petraco,
MS, RN, PNP
PO Box 306
Deer Park, NY 11729

Comment.—This is in response to Dr Jones and to Dr Fikar and Ms Koslap-Petraco, the latter of whom state, "We are quite surprised that a letter such as Dr Jones' would be printed in *AJDC*," and continue to offer their view of the Pediatric Forum. In our view, the Pediatric Forum is a place for any concerned reader to offer observations, comments, critiques, and queries concerning published material in *AJDC*, or to discuss issues that affect infant, child, or adolescent health care. The Editor does not make judgements concerning the viewpoints of the writer, even if he disagrees with that viewpoint. Instead, our goal is to permit a wide range of opinions to be expressed, and, if the letter concerns a prior publication, to offer the author an opportunity to respond. We believe it is perfectly appropriate to publish Dr Jones' letter, as we do the authors' response. Our readers can reach their own conclusions as to the viewpoints expressed.

VINCENT A. FULGINITI, MD
Editor, *AJDC*

The Problem of Indigent Children: Shutting Off the Supply

Sir.—There is abundant documentation of the problems of indigent children; many are from one-parent families, many are homeless, and a large proportion are from unplanned and often complicated pregnancies. In addition, there are many thousands of pregnancies aborted annually. All agree that women should be able to decide when they wish to become pregnant. If this were the case, many fewer pregnancies would occur, particularly among indigent young women and adolescent girls. Current methods of contraception are not providing the answer to the problem due to a variety of reasons relating to cost, effectiveness, and accessibility in the indigent population.

One method that is not widely practiced is available, effective, and, once initiated, requires no further effort on the part of the individual. This method is the implantation of a progesterone derivative (Norplant, Wyeth-Ayerst Laboratories, Philadelphia, Pa) subcutaneously in a depot form. The agent has been widely used in the United States and other countries by thousands of women. Only minimal side effects have been documented. The implant may be removed at any time, with fertility restored. The current cost is approximately $500 per implantation.

Previous debate has centered about its availability, particularly to indigent patients. This proposal seeks to remedy that situation. Every woman registering for aid under welfare programs, such as Aid for Dependent Children, and for health care under Medicaid or Public Health Services would be required to sign the following statement:

"I have been counseled about the use of Norplant for prevention of pregnancy and the option for its use has been made available to me. I have decided to accept _____ or refuse _____ this method of birth control." The decision to accept or refuse would have no impact on provision of requested services. There should be absolutely no element of pressure to use Norplant. It would only be required that the individual understand the availability of this form of contraception. Although many indigent women desire pregnancy, a large number do not, and it is likely that this program would reduce significantly the number of unwanted pregnancies, particularly in young, unmarried women. This group has a large number of complicated pregnancies; abortions; and births of infants at risk from prematurity, intrauterine exposure to toxic substances, and prenatal problems.

Legislation establishing this policy would obviously require appropriation of funds to make Norplant available to those requesting it. Certainly, the $500 cost per person would be quickly offset by the savings from fewer unwanted pregnancies and their consequences, including care for an ever-increasing number of unwanted indigent infants and children.

This concept will no doubt offend those who oppose contraception on various religious and moral grounds. However sincere and well-motivated these concerns, society is now at a point at which the magnitude of the problem should override the imposition of these views on individuals who do not share them. The proposal should not offend those who are "pro life" since, in fact, it will prevent several hundred thousand abortions, induced and spontaneous, now occurring yearly.

A valid criticism is that this method of contraception does not prevent and may even enhance the occurrence of sexually transmitted diseases, including acquired immunodeficiency syndrome. While this may be true, the limited use of barrier forms of contraception at present makes any increase in risk quantitatively not very significant. This disadvantage is offset in a major way by prevention of pregnancy in infected mothers, thereby reducing the number of infants born with acquired immunodeficiency syndrome, syphilis, and other diseases resulting from intrauterine transmission of the infecting organism. This mode of infection accounts for more than 90% of cases of acquired immunodeficiency syndrome in infants and children.

Implementation of this proposal will require courage based on foresight and will most likely not be embraced by the fainthearted among our policy makers. Nevertheless, thoughtful consideration will reveal it to be an enormous step toward solution of a major national social problem that is compromising a large section of our present and, more importantly, our future population.

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Is There a 'Gold Standard' for Drug Detection in Pregnancy?

Sir.—Maynard and colleagues[1] discuss a very timely and clinically important issue, ie, detection of drugs of abuse in pregnancy and in the newborn. Their study describes the use of meconium samples, which are easier to collect than urine and provide information about drugs that may have been used for at least several weeks prior to delivery. However, the authors state that "meconium testing predicted a positive urine test in 14 of 17 cases . . . and predicted a negative urine test in 10 of 11 cases . . . " They refer to these as the positive and negative predictive values of the test.

Positive predictive value is defined as the "probability of disease in a pa tient with a positive (abnormal) tes result." Negative predictive value is defined as the "probability of *not* hav ing the disease when the test result is negative (normal)."[2] To determine whether the patient has the disease (ie, whether the baby has been ex posed to drugs in utero), one must compare the meconium test results with "the gold standard." Urine testing for drugs in pregnancy or in the newborn is far from a gold standard since many drugs are metabolized rapidly and cleared from the body in a few hours or days. It is unfortunate but there is no gold standard for drug detection in the prenatal or neonatal period.

Positive predictive value and negative predictive value are defined as follows:

$$PV_{pos} = TP/(TP+FP) \text{ and}$$
$$PV_{neg} = TN/(TN+FN)$$

where TP indicates true positives; FP, false positives; TN, true negatives; and FN, false negatives. The predictive value of a test depends on the prevalence of disease in the population being examined. As the prevalence of disease increases, the positive predictive value of a test also increases. The prevalence of drug use is higher in the sample studied by Maynard et al (women *suspected* of drug abuse) than in the general population of *all* pregnant women; thus, the positive predictive value of the test in the sample studied by Maynard et al is higher than it would be in the general population.

Maynard and colleagues are to be commended for studying meconium for drug detection in newborns since it is easy to obtain and may give information about drugs that have been ingested over at least the last few weeks of pregnancy. However, we are still a long way from having a valid and reliable test (a gold standard) to detect drug abuse in pregnancy.

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1. Maynard EC, Amoruso LP, Oh W. Meconium for drug testing. *AJDC.* 1991;145:650-652.
2. Fletcher RH, Fletcher SW, Wagner EH. *Clinical Epidemiology.* Baltimore, Md: Williams & Wilkins; 1988:54-61.

Call for Clarification of Vitamin D Recommendations

Sir.—I have two questions concerning the letter by Bhowmick et al[1] that appeared in the February 1991 issue of AJDC. First, in the last paragraph of the letter, the authors stated, "Although it may be true that some breast-fed infants do not routinely need vitamin D supplements, we do recommend 400 IU of supplementary vitamin D per day in all breast-fed black infants regardless of geographic location." I want to know what the authors meant by "some."

The second issue pertains to the quality of evidence that "proves" that this regimen adequately prevents rickets. No reference was given for that claim, and I am eager to know the source.

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1. Bhowmick SK, Johnson KR, Rettig KR. Rickets caused by vitamin D deficiency in breast-fed infants in the southern United States. *AJDC.* 1991;145:127-130.

In Reply.—We thank Dr Blandino for the letter and the opportunity to clarify the two points that he addresses. Vitamin D supplementation may not be necessary for those infants who are breast-fed for 6 months or less,[1,2] whose mothers have either adequate stores or synthesis or intake of vitamin D while breast-feeding,[3] and who receive adequate exposure to sunshine.[4] Although we recommended vitamin D supplementation for all breast-fed black infants, in practice, we supplement the recommended dosage of vitamin D in all breast-fed infants.

An intake of 400 IU of vitamin D is the standard recommended daily allowance for infants for prevention of rickets.[5,6] The Food and Nutrition Board of the National Academy of Science also recommends 400 IU of vitamin D daily for children up to age 18 years.[6] An intake of 400 IU of vitamin D is safe, nontoxic, and appropriate.[5,6] In fact, as little as 100 IU of vitamin D may prevent rickets.[6]

To our knowledge, there has been no published report that vitamin D deficiency is the cause of rickets in breast-fed infants receiving the recommended dosage of 400 IU of vitamin D daily. Exceptions to that may be vitamin D malabsorption (fat malabsorption), vitamin D resistance state, significant liver and kidney diseases, and drugs interfering with vitamin D synthesis and metabolism.

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1. Greer FR, Marshall S. Bone mineral content, serum vitamin D metabolite concentration and ultraviolet B light exposure in infants fed human milk with and without vitamin D_2 supplements. *J Pediatr.* 1989;114:204-212.
2. Birkbeck JA, Scott HF. 25 Hydroxycholecalciferol serum levels in breast fed infants. *Arch Dis Child.* 1980;55:691-695.
3. Bachrach S, Fisher J, Parks JS. An outbreak of vitamin D deficiency rickets in a susceptible population. *Pediatrics.* 1977;64:871-877.
4. Specker BL, Valaris B, Hertzberg V. Sunshine exposure and serum 25-hydroxy vitamin D concentration in exclusively breast fed infants. *J Pediatr.* 1985;107:372-376.
5. Mimouni F, Tsang RC. Disorder related to vitamin D, calcium or phosphorus deficiency. In: Kaplan SA, ed. *Clinical Pediatric Endocrinology.* 2nd ed. Philadelphia, Pa: WB Saunders Co; 1990:442-448.
6. Chesney RW. Requirements and upper limits of vitamin D intake in the term neonate, infant and older child. *J Pediatr.* 1990;116:159-166.

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References: 1. Sandler RB, et al: *Am J Clin Nutr* 1985;42:270-274. 2. Rubin K: *Pediatric By-Line* 1985;4(3):1, 4-6. 3. Marston R, Raper N: *National Food Review* 1987;36:18-23. 4. Heaney RH: *The Physician and Sportsmedicine* 1987;15:83-88.

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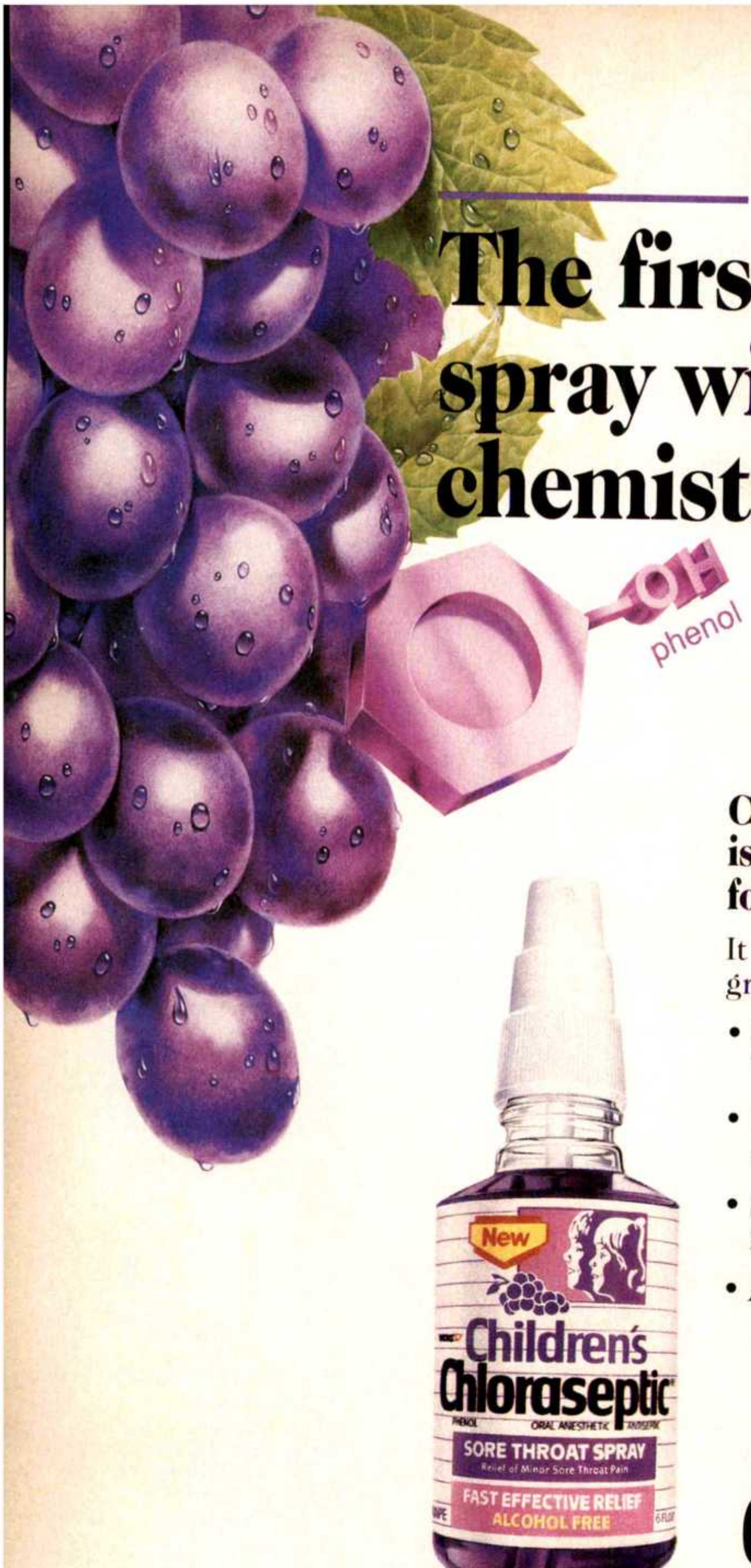

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What Is Pediatrics?: Prenatal Medicine to Young Adult Care

Vincent A. Fulginiti, MD

In 1969, when I became chairman of the Department of Pediatrics at the University of Arizona, I visited the offices of pediatricians in Tucson. On one of these visits, I noticed a young man, approximately 18 years old, sitting in the reception area as both of us waited for the pediatrician. Somewhat surprised, I learned that he was there for his precollege physical examination. He had always been cared for by this pediatrician, and wished to continue receiving care from this pediatrician at this point in his life. My surprise was engendered by the "common wisdom" at the time that individual children, or their parents, wished to discontinue pediatric care when adolescence was reached or shortly beforehand. In the hospitals in which I had practiced, children were no longer admitted to pediatric units after approximately age 12 years, reflecting this commonly held thesis.

As we planned our department and the new hospital, we decided to accommodate the wishes of our patients, ie, that they continue to be cared for by pediatricians, whom they trusted, liked, and believed were more in tune with their needs than were nonpediatric physicians. Young men and women with chronic diseases, such as cystic fibrosis, congenital heart defects, and hypogammaglobulinemia, actually switched back to pediatricians after encounters with other physicians. They did so despite admixture with infants and younger children, thought by adult caretakers and physicians to be a deterrent to the adolescents and young adults considering continued care from pediatricians. Of course, we made every effort to provide appropriate environments for them in the hospital and the clinic, but that often proved impossible because of shortage of suitable space. Nevertheless, they continued to flock to our units and did not wish, in the main, to be hospitalized or cared for in adult units in the hospital or clinic. It was not uncommon for us to have individuals 20 to 30 years old in our pediatric wards and clinics. They were most comfortable, as were our faculty.

In subsequent years, the American Academy of Pediatrics, responding to actual practice, publicly proclaimed that the scope of pediatrics ranged from prenatal care to care for young adults, and that adolescent medicine was a legitimate part of this practice. The Academy gave prominence to adolescent medicine in its publications, sections, committees, and continuing education programs. Likewise, pediatric educators across the country began to include principles of adolescent medicine in junior medical student instruction, senior medical student elective rotations, and residency programs. Many departments developed sections of adolescent medicine, and national professional societies recognized the needs of members who devoted all or a large part of their academic or practice activities to this age group's problems and concerns.

These recollections came back to me in full force recently when I recognized that little advertising in *AJDC* was related to adolescents or young adults. This despite the fact that we publish many articles addressing issues of adolescent and young adult health, have a board member whose specialty is adolescent medicine (Elizabeth McAnarney, MD), and publish editorial statements that have consistently reflected our readers' and authors' interests in adolescents and young adults. In our May 1991 issue addressing the lack of adequate health care for the poor and underserved, we made a special point to include articles describing the plight of adolescents and young adults in these categories.

So, when I ask rhetorically, "What is pediatrics?," I imply that everyone already knows that the discipline includes a broad range of duties—from prenatal counseling, through care of newborns, infants, and young children, to concern with health issues of adolescents and young adults. However, some in society have not gotten the message, although many of our young adults have tried to deliver it, and the American Academy of Pediatrics and *AJDC*, among others, have heralded it.

Pediatrics is that discipline relating to the basic science of developmental biology and includes the period from fetal development through young adulthood. It is not so much chronologically age limited as it is related to the needs of patients at any age through young adulthood. That young man sitting in the pediatrician's office knew what he needed, and he received it from the doctor he trusted and respected. He, and countless others, have sought the kind of care and attention that they believed their conditions or health needed.

Pediatricians have responded by ensuring that they have the requisite knowledge and skills to care for this group of patients. For years, continuing education courses have emphasized drug abuse, sexual counseling, illnesses prevalent in adolescents, and skills needed to care for adolescents and young adults, such as those required for pelvic examination. Pediatricians are knowledgeable about the hormonal changes of adolescence, the continuing manifestations of chronic diseases in this age group, and the emotional and other psychological characteristics and challenges encountered by the maturing individual. They are equipped to deal with health and disease in patients in this age group, and these patients are prepared to be cared for by them.

AJDC contributes to this effort by publication of articles that discuss issues important to adolescents and young adults. Endocrinological, gynecologic, dermatologic, and nutritional changes; drug and substance abuse; and accidents are some of the important issues of adolescent and young adult health presented in *AJDC*.

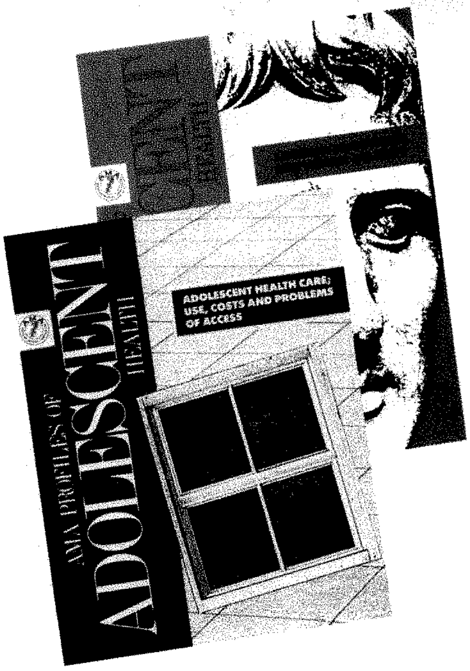
Imagine

Imagine them all getting better. All through the hospital, the children get better, their breathing gets easier, they poke their heads out of the oxygen tents and take deep breaths of room air. They pull the IVs out of their hands, their feet, their chests, their heads. No one needs antibiotics; the evil bacteria are dead. No more fevers, no more wheezing, above all, no more pain.

Imagine them pouring out the front doors, the big ones now carrying the babies, reaching down to hold the hands of the toddlers. The whole pack disappearing down the street, leaving the hospital, with its humming lights and beeping monitors, leaving it behind.

The hospital is active but abandoned, like a factory newly automated, or perhaps like something more sinister. Like a ghost ship. No more chemotherapy, no more dialysis, no more ventilators, no more fighting to pull air in against a tight swollen throat, no more inflammation of the brain, no leukemia, pneumonia, croup, seizures. No fevers of unknown origin, no occult malignancies, no failure to thrive. The children are out of sight now, heading home.—Perri Klass

Klass P. *Other Women's Children.* New York, NY: Random House Inc; 1990:283-284.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Autologous Transfusions for Neonates Using Placental Blood

A Cautionary Note

In this issue of *AJDC*, Anderson et al[1] review previous studies and report additional information to support the collection and storage of placental blood as a source of autologous red blood cells (RBCs) for neonates who require transfusions. It is important to note that studies to date have focused primarily on developing techniques to obtain placental RBCs. No definitive clinical information exists to establish the feasibility, efficacy, and safety of placental RBCs in the actual treatment of neonates. Accordingly, the authors appropriately caution that further studies are mandatory before this technique is applied in clinical settings. To emphasize this point, I will summarize a few of the issues that must be addressed by future studies.

Efficacy and safety must be established before a medical intervention is applied in clinical practice, regardless of how appealing it might be. Because the safety of transfused blood is currently of paramount importance, it will be discussed first. In general, the safety of autologous blood is superior to that of blood obtained from homologous donors. However, the relative safety of placental blood as a source of autologous RBCs vs banked units from homologous donors must be carefully assessed by weighing all infectious disease risks.

Because of the many changes in donor screening and testing implemented recently to increase the safety of homologous blood, it is difficult to accurately predict the risks of acquiring a transfusion-transmitted infection. It is estimated that the risk of acquiring human immunodeficiency virus is between one in 100 000 (0.001%) and one in 1 million (0.0001%) per each transfusion. For hepatitis B, the risk is one in 50 000 (0.002%), and for non-A, non-B hepatitis, it is one per 100 (1.0%) to one per 500 (0.2%) transfusions. Thus, the risk of viral infections acquired from homologous transfusions has been markedly reduced, and it is important not to substitute other dangers in attempts to avoid these rare events.

To illustrate this point, the rate of bacterial contamination of units of banked homologous blood is quite small. The mean rate of bacterial contamination was 0.31% over 10 years, during which time a mean of 2282 units were studied annually.[2] In contrast, the 12% (seven of 58 placental blood samples) rate of positive bacterial cultures reported by Anderson et al[1] is alarming! In three of the seven units, positive cultures probably represented the presence of bacteremia in the infant and do not reflect a flaw in the collection technique. After eliminating these samples, four (7.3%) of the remaining 55 placental samples were contaminated with common vaginal flora, a rate similar to the 9.7% reported by earlier investigators.[3] The true rate of bacterial contamination in units of placental blood cannot be determined by the small numbers of units reported to date.

Scientifically, the issue might be resolved by culturing several hundred samples. Viewed in a regulatory and legal perspective, however, vastly more extensive data will undoubtedly be required to satisfy all interested parties; the Center for Biologics Evaluation and Research of the Food and Drug Administration considered changing national blood banking practice because 10 cases of *Yersinia* contamination of RBC units were reported during a time in which approximately 50 million transfusions were given, an adverse event rate of one per 5 million transfusions (0.00002%).[4] Thus, the risk of possible bacterial contamination of placental blood must be carefully balanced against the benefit of avoiding homologous RBCs. Parents should be made aware of this information as they decide whether to give consent for their neonates to receive placental RBCs.

Another consideration related to safety is the possibility that placental blood might be contaminated with blood of the mother, a situation that conceivably could lead to fatal graft-vs-host disease. Although this sequence of events is unlikely, it is of interest to document the rate of maternal blood contamination, using the Kleihauer-Betke stain, as techniques to collect placental blood are developed. Placental RBCs, found to be contaminated with maternal blood, represent a transfusion from a first-degree relative and, by current practice, should be irradiated prior to transfusion. As a final safety issue, the quality of placental RBCs following storage must be established. Several metabolic and biologic differences are exhibited by RBCs from fetuses/neonates compared with cells obtained from adults. Conceivably, placental RBCs could develop "storage lesions" that render them relatively unsatisfactory and possibly dangerous as a transfusion product.

As safety questions are resolved, it is also important to define the efficacy of placental RBC transfusions. Autologous transfusions are most efficacious when the need for homologous blood is eliminated completely. It is unlikely that placental RBC transfusions will eliminate the need for homologous transfusions in most neonates with birth weights of less than 1500 g. In our experience,[5] 78% of infants with birth weights of less than 1500 g required RBC transfusions. Among those transfused, a mean(±SD) 10.0±8.3 transfusions were needed, with 82% of infants receiving more than four RBC transfusions. Similar data have been reported by other investigators.[5] Anderson et al[1] found that 87% of placental collections provided sufficient blood for at least one 10-mL/kg transfusion, but only 53% provided enough for two or more transfusions. Because of the relatively small volumes collected, the majority of tiny, premature neonates likely will require additional measures, such as treatment with proper doses of recombinant erythropoietin and use of limited-exposure donor programs.[5]

The transfusion of placental RBCs for some neonates may find a niche within this overall armamentarium. In particular, renewed attention should be given to transfusions from the placenta to the neonate *before* the umbilical cord is severed. It has been suggested that cord clamping be delayed until 30 seconds after birth, during which time the neonate is held 20 cm below the placenta.[6] Although this practice is not without potential problems (eg, hyperviscosity due to erythrocytosis, transfusion of maternal blood, and delay in resuscitation), it would avoid some of the problems of collection and storage.

The collection, storage, and transfusion of placental RBCs is a topic of great interest to physicians and parents of premature infants. It is worthy of additional investigations. Because premature infants require many RBC transfusions, the possibility of using autologous blood should be explored, providing that the risks of doing so do not exceed those of transfusing homologous blood. Concerns can be raised about the high rate of bacterial growth, contamination with maternal blood leukocytes, and quality of placental RBCs during short-term storage and, finally, whether a significant number of homologous transfusions actually will be eliminated by the use of placental RBCs. It is important not to view the possibility of transfusing autologous RBCs so enthusiastically that transfusion practices change before unanswered questions are resolved, and the true balance of benefits and risks is defined.

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Bones of Today, Bones of Tomorrow

See also p 111.

With improving knowledge and advancing technology, physicians who care for the young are assuming an expanding role in the prevention of diseases that become evident during adulthood, but have their origins in childhood and adolescence. Cardiovascular disorders such as essential hypertension and atherosclerosis are no longer exclusively the purview of internists. Modifiable risk factors can be identified and improved in the pediatric age group with the goal of preventing or ameliorating heart disease in later life. Likewise, the prevention of osteoporosis, often deemed a geriatric disorder, may now be considered the legitimate domain of pediatricians.[1] Recent studies point to the significance of achieving adequate peak bone mass in girls during the growth period, prior to their obligatory, accelerated postmenopausal bone loss.[2] Adolescents are particularly noteworthy in this regard, since almost half of the adult skeletal mass is formed during the second decade and calcium accumulation normally triples during the pubertal growth spurt.[3] Maximal deposition of mineral in the skeleton during the growth phase can offset the subsequent inexorable loss of bone that accompanies aging, especially in women.

However, we still know little about the mechanisms that increase bone mass in adolescents[4]; much more is known about the factors associated with bone loss. Immutable genetic factors are probably the strongest influence on bone mineral acquisition and loss, but low weight, inadequate calcium intake, inadequate mechanical forces on bones, and menstrual irregularities are the most commonly recognized modifiable factors related to the achievement of suboptimal bone mass.[2] All known risk factors typically account for less than half the variance in bone mass in a population, and no combination of clinical risk factors yet identified is capable of accurately predicting fracture risk better than the measurement of reduced bone mass (osteopenia) in an individual.[5] Therefore, direct measurement of bone mass, expressed either as content or density of mineral, becomes central to any intervention to assess bone status or to monitor changes with treatment.

In this issue of *AJDC,* White and colleagues[6] report two important findings in their cross-sectional study of bone mineral density (BMD) of the lumbar spine and femoral neck in 28 eumenorrheic late adolescents, and of the lumbar spine in eight younger adolescents with amenorrhea (five due to anorexia nervosa and three due to exercise). First, appreciable increases in BMD were not detected at either site in the eumenorrheic subjects over the 15- to 21-year age range studied, suggesting that peak BMD in their sample may be achieved by age 15 years. Second, although the amenorrheic patients had lower spinal BMD, the statistical significance of this difference was eliminated by controlling for weight. Low weight per se had a significant relationship to decreased BMD in adolescents, as has been demonstrated recently by others.[7,8] An understanding of the new technology presently available to measure various sites and aspects of bone mineralization is a prerequisite to the rational treatment of disturbances in bone mass acquisition in the future.

To be clinically useful in identifying osteopenia, a method to quantify bone mineral should be noninvasive, safe, precise, accurate, and accessible, and should provide information that relates measurement to subsequent risk of fracture at a reasonable cost.[9] No assessment tool presently available meets all of these criteria. Single photon absorptiometry (SPA) measures mineral content in grams of bone mineral per square centimeter scanned in the appendicular skeleton (usually the nondominant distal radius), using a monoenergetic photon source such as iodine 125. Radiation dose (less than 10 mrem), degree of precision (1% to 5%), and accuracy (1% to 5%) associated with it are all favorable. However, SPA assesses predominantly cortical bone that is less metabolically active and less commonly fractured than sites such as the spine or hip. Nonetheless, numerous studies have demonstrated a strong relationship between this measure and subsequent fracture risk in both the hip and spine.[10-12] In most studies, a decrease of 1 SD in BMD as measured by SPA has been associated with a 50% to 100% increase in the incidence of fracture, greater than the increased risk of heart attack observed with a 1-SD increase in serum cholesterol.[5]

Dual photon absorptiometry (DPA) uses gadolinium 153, a radioisotope that emits photons of two different energy levels, to determine total body, spine, or hip BMD, also expressed in grams per square centimeter. Dual photon absorptiometry is similar in precision to SPA, with a slightly lower degree of accuracy and slightly higher radiation dose. Unlike SPA, however, DPA can over time quantify changes in BMD associated with metabolic bone disorders. This greater sensitivity to change arises because DPA can determine BMD in predominantly spongy, trabecular bone, with an eightfold greater turnover rate than compact, cortical bone. Thus, the earliest evidence of generalized disturbances in bone metabolism, such as occurs with low weight, inadequate calcium intake, low sex steroid, or high cortisol level, appears in trabecular bone.

Quantitative computed tomography, either single or dual energy, has the greatest ability to selectively measure trabecular BMD in the spine. Despite this advantage and a degree of precision and accuracy comparable with those of DPA and SPA, the routine use of quantitative computed tomography cannot be justified in girls of reproductive age, given its radiation dose of up to 1000 mrem,[5] especially if serial measurements are planned. The same can be said for neutron activation analysis, which can result in even higher radiation exposures.[9]

White and colleagues[6] used dual energy x-ray absorptiometry to determine BMD. In principle, it is similar to DPA, but with numerous advantages over other techniques. Because of significantly greater photon flux, it has much greater resolution, precision, and accuracy than either SPA or DPA. However, the radiation exposure is significantly less than with other methods (less than 3 mrem).[9] This is the only method offering lateral spine BMD determination, which allows for removal of the posterior (predominantly cortical) elements from analysis, isolating vertebral body trabecular bone. In addition to safety, the cost is only slightly more than that of DPA, and a scan in the fast mode can be completed in under 10 minutes. Because this method appears to have the greatest advantages and the fewest disadvantages of any available technique, its use in the determination of BMD, when indicated, is encouraged.

In the future, bone mass determination for clinical use with quantitative magnetic resonance imaging or ultrasonographic methods will become available. However, at this time, they remain experimental techniques in the evaluation of BMD. Ultrasonography is especially attractive since it is widely available, safe, and has numerous other applications likely to increase patient and parent acceptance.

Armed with knowledge of the methods available to assess bone mass, under what circumstances should a clinician consider ordering such a test? A number of factors must be taken into account in making this decision. First, there are no normal BMD standards for individuals younger than 21 years. Although recent studies of BMD have reported using dual energy x-ray absorptiometry in normal subjects aged 1 to 18 years, they do not provide consistent findings. For example, in keeping with the report of White and colleagues,[6] Bonjour and colleagues[13] found that lumbar spine BMD in normal girls did not increase appreciably after age 15 years. However, the mean (±SD) BMD of 15-year-olds in the former study was 1.26±0.05 g/cm², in contrast to 1.01±0.03 g/cm² (approximated from graph) in the latter. Similar differences were found throughout the 15- to 21-year age range studied. Although the sample size in each age category in the study by White et al was small ($n = 4$ to 7), the SD was also small, especially in the 15- through 18-year age group. Therefore, the large difference in lumbar BMD reported for 15-year-old girls in these two studies raises serious questions about the generalizability of one or both of the samples to a population of normal 15-year-old girls.

Some of this difference may be a measurement artifact, since the two studies used instruments from two different manufacturers (Lunar Radiotion Corp, Madison, Wis, and Hologic Inc, Waltham, Mass). Glastre and colleagues[14] used an instrument from the same manufacturer as Bonjour et al[13] and obtained similar peak BMD measurements during adolescence. However, for girls, the peak was reached by age 12 years in the study by Glastre et al, but not until age 15 years in the sample studied by Bonjour et al. Correcting for pubertal status tended to smooth out these differences. Comparison of the age or stage of sexual maturity at the achievement of peak BMD is impossible in the study by White et al because subjects younger than age 14 years were not included.

Given the high priority that has been given to the prevention of adult osteoporosis, densitometers will undoubtedly become more available in the future. Prior to widespread clinical use in adolescents, however, the issues mentioned above must be addressed. Large numbers of adolescents will be required to develop normal standards, since it will be necessary for groups to be broken down by race (blacks have higher BMDs than whites), age (BMD increases at least until age 15 years), sexual maturity rating (BMD increases markedly between stages 3 and 5) and sex (boys have higher BMDs than girls at comparable stages of sexual maturity). Weight should not be used as a reference, since it has been demonstrated that low weight is associated with low BMD, possibly leading to the acceptance of suboptimal BMD as normal. Also, some cross-sectional studies report no increase in BMD after late adolescence, whereas larger studies have found increases until age 35 years.[2]

A second point to consider before obtaining a BMD measurement in an adolescent is the recommended clinical use of bone densitometry in adults. Although the use of densitometry as a screening tool is controversial,[15] there is relative agreement regarding clinical indications for individual patients. An ad hoc subcommittee of the Scientific Advisory Board of the National Osteoporosis Foundation[16] suggested the following four clinical indications for densitometry based on scientific evidence published in the literature: (1) estrogen deficiency; (2) vertebral abnormalities or roentgenographic osteopenia; (3) long-term glucocorticoid therapy; or (4) primary asymptomatic hyperparathyroidism. All of these indicators relate to mechanisms of increased bone loss and were developed primarily for adults. Since that report, additional potential indications for densitometry have been suggested, including the monitoring of response to treatment and the identification of patients who lose bone faster than normal and those with secondary hyperparathyroidism due to gastrointestinal malabsorption or renal disease.[5]

How these indicators for bone densitometry will be extrapolated to adolescents, once normal standards are established, is unclear. Until recently, the most common metabolic bone disease in the pediatric age group was rickets, resulting in osteomalacia rather than osteoporosis.[17] For contemporary adolescents, estrogen deficiency generally is indicated by amenorrhea. Although conditions such as Turner syndrome or craniopharyngioma are causes, the most common causes of prolonged amenorrhea in adolescents are weight loss and excessive exercise. Thus, adolescents with anorexia nervosa,[7] dancers,[8] and long-distance runners[18] are at risk of having low BMD on the basis of amenorrhea and low body weight. The complex nature of the interactions of various factors related to BMD must be appreciated, however, since athletes who remain eumenorrheic can actually have a higher BMD than normal.[18] Furthermore, recent data indicate that even minimal disturbances in menstrual cycles (asymptomatic disturbances of ovulation with regular menses) can be associated with decreases in spinal BMD, suggesting a previously unrecognized role of progesterone in the maintenance of bone health.[19]

Vertebral abnormalities suggesting osteopenia on routine roentgenography are uncommon in the pediatric age group. However, long-term glucocorticoid treatment for various medical conditions is a common occurrence among adolescents. With the high degree of precision and safety of techniques such as dual energy x-ray absorptiometry, data regarding low or decreasing BMD could be used in making clinical decisions related to pharmacologic treatment of chronic illnesses. Likewise, hyperparathyroidism in adolescents is most commonly secondary to another medical condition, and densitometry could play a similar role in evaluating bone health in this clinical situation. It must be kept in mind that boys, as well as girls, are vulnerable to these causes of osteopenia. Thus, there are parallel conditions in adolescents that could be considered indicators for bone densitometry, such as menstrual cycle disturbances, long-term glucocorticoid treatment, and secondary hyperparathyroidism. Although there appears to be a relationship between calcium intake and BMD,[4,20,21] dietary deficiencies cannot yet be considered an indication for densitometry, unless of course there is an attendant condition such as anorexia nervosa. If efforts to maximize the peak bone mass by means of normal exercise and calcium intake in adolescents become public health policy in the future, bone densitometry may be a useful adjunct to determine the effectiveness of such interventions, especially for girls with a family history of osteoporosis.[22]

The third point that must be kept in mind by the clinician considering densitometry is how the information will be used in the treatment of the underlying condition.[23,24] An understanding of the limitations of the measure, its precision, and its ability to detect change over time, as well as the clinical implications of normal and abnormal results, is required. A BMD determination must be considered in the context of an individual patient. However, as mentioned above, it has the potential of providing important data regarding a patient's bone mineral status that is presently not included in the decison-making process. Unfortunately, the consequences of low bone mass may not become evident for decades, years after the physician who cared for the young person is no longer involved. The evidence regarding the risk of osteoporosis as a function of premenopausal bone mass clearly supports the detection and reversal of suboptimal peak bone mass.[25]

This raises a final consideration in the use of bone densitometry, namely, the limited options available to clinicians in the development of healthy bones. There is no treatment presently available that reliably reverses osteopenia in adults. Therefore, efforts have been directed at preventing bone loss; interventions have included improved calcium nutriture,[4] physical activity,[26] and sex steroid replacement,[27] without remarkable success in any population of adults. More specific treatment with bone resorption inhibitors such as calcitonin or diphosphonates remains experimental at this time.[28] These limitations in adult populations make any opportunity to increase bone mass in pediatric patients all the more exciting. The growth potential inherent in the young imparts a theoretical potential to actually increase BMD, especially if it has decreased due to illness. Encouraging results in this respect were recently reported by Bachrach and colleagues,[29] who found an increase in BMD in some adolescent girls during recovery from anorexia nervosa.

Bone densitometry will certainly become more available, precise, safe, and standardized over time. Clinical indications for its use in adolescents will be more clearly delineated as well. By attending to the needs of growing bones in our patients, perhaps we can prevent at least some cases of brittle bones in the future.

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Pediatric Pathology

In recent years, the value of pathology, the queen of medical sciences, has been challenged by new sophisticated imaging and biochemical procedures. Nonetheless, for definitive diagnosis the pathologist continues to have the last word.

The editor and editorial board of *AJDC* have long recognized the educational value of pediatric radiology and pediatric dysmorphology, especially as they pertain to pediatric diagnosis and treatment. Departments examining the significance of these special diagnostic aids have become regular features of *AJDC*. More recently, *AJDC* has added Pediatric Perspectives and Pediatric Legal Medicine to its list of departments. The editorial board has decided that now is an appropriate time to challenge the reader by presenting case examples of conditions diagnosed or misdiagnosed by clinicians that were finally verified or disproven with tissue or clinical laboratory examination. Such exercises are especially pertinent now, when the postmortem examination is increasingly uncommon despite well-documented evidence of erroneous final diagnoses made after extensive clinical examination that were only corrected later after thorough autopsy evaluation.[1,2] Recently, the special importance of postmortem examinations has been demonstrated in cases of sudden unexplained infant death.[3]

To quote Sir William Osler, "To investigate the causes of death, to examine carefully the condition of organs, after such changes have gone on in them as to render existence impossible, and to apply knowledge to the prevention and treatment of disease, is one of the highest objects of the physician. . . ."[4] With this issue of *AJDC*, we inauguarate the Pathological Case of the Month. Common conditions with unusual findings, conditions in which errors are likely to be made, uncommon conditions with striking anatomic or clinical pathologic findings, or findings correcting old diagnoses are suitable for consideration. Photographs of tissues, photomicrographs, electronmicrographs, roentgenograms, computed tomographic scans, magnetic resonance images, and ultrasound studies are welcome, as are clinical pathologic data.

The broader the participation in this new department, the more educational and enjoyable this section of *AJDC* is likely to be. We welcome your contributions.

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and Pediatrics
University of Wisconsin
Center for Health Sciences,
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600 Highland Ave
Madison, WI 53792

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ARCHIVES OF GENERAL PSYCHIATRY

Nicotine Dependence, Major Depression, and Anxiety in Young Adults

Naomi Breslau, PhD; M. Marlyne Kilbey, PhD; Patricia Andreski, MA
(*Arch Gen Psychiatry*. 1991;48:1069-1074)

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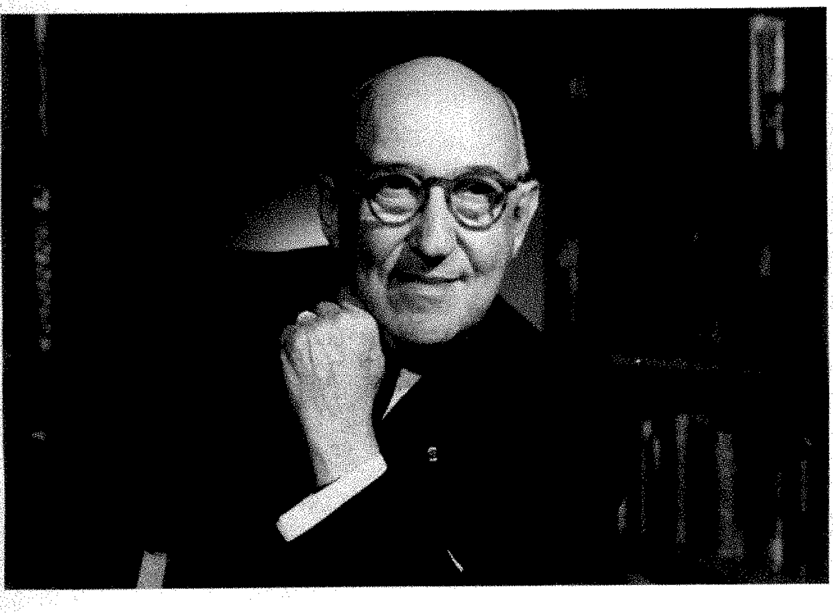

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CONSIDER TREATMENT WITH VIRAZOLE

In infants and young children hospitalized with severe lower respiratory tract RSV infections, Virazole remains the standard of care.

The presence of the following underlying conditions may increase the severity of the infection and its risk to the patient.[1]

- Congenital heart disease
- Bronchopulmonary dysplasia
- Other chronic lung conditions
- Certain premature infants
- Immunodeficiency
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- $Pa0_2 < 65$ mmHg
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- Less than 6 weeks of age
- Multiple congenital anomalies, neurologic, metabolic diseases
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PRESCRIBING INFORMATION

WARNING: RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still in development.

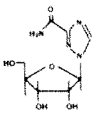
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16 μg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 μM, with a mean concentration of 0.76 μM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 μM, with a mean concentration of 6.8 μM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possible emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C3T3 cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD_{50} in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION:

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml widemouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

HOW SUPPLIED:

Virazole® (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

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ADVERTISING REFERENCES:

1. Adapted from "Policy statement. Ribavirin therapy of respiratory syncytial virus." American Academy of Pediatrics Committee on Infectious Diseases. 1986-87.

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Bone Mineral Density in 15- to 21-Year-Old Eumenorrheic and Amenorrheic Subjects

Catherine M. White, MD; Albert C. Hergenroeder, MD; William J. Klish, MD

• The purposes of this study were to compare the lumbar spine bone mineral density of eumenorrheic and amenorrheic white subjects aged 15 to 21 years, and to describe the femoral neck bone mineral density in the eumenorrheic subjects. Twenty-eight eumenorrheic females had lumbar bone mineral density (mean±SD) of 1.213±0.117 g/cm^2, and femoral neck bone mineral density of 1.032±0.092 g/cm^2 measured with dual energy x-ray absorptiometry. Bone mineral density at neither site was related to age, energy intake, or calcium intake. Femoral neck bone mineral density was related to energy expenditure. Body composition was measured with total body electrical conductivity, and bone mineral density at both sites was related to body weight as much as fat-free mass. Eight amenorrheic subjects had a lumbar spine bone mineral density of 1.057±0.113 g/cm^2, which was lower than in the eumenorrheic group. However, when controlling for weight, this difference was not significant. Peak lumbar and femoral neck bone mineral density may be reached at midadolescence.

(*AJDC.* 1992;146:31-35)

Although osteoporosis is a disease primarily of older women, its onset may be in adolescence and early adulthood in young women with estrogen and/or progesterone deficiency, such as those with hypothalamic amenorrhea.[1-8] Women who reach age 20 years and have missed 50% of their expected menstrual periods are likely to have reduced bone density.[9] In healthy females, bone mass increases throughout childhood with a marked increase in early puberty.[10-12] However, there is relatively little information on bone mineral density (BMD) in females in the 15- to 21-year age group, an age group in which women are becoming increasingly athletic and eating disorders appear.[6,12] We are not aware of any reports of femoral neck BMD in healthy white females aged 15 to 21 years. The purpose of this study was to compare the lumbar BMD in 15- to 21-year-old eumenorrheic and amenorrheic white subjects using dual energy x-ray absorptiometry and to describe the femoral neck BMD in the eumenorrheic subjects. In addition, we examined the relationship between lumbar and femoral neck BMD and body composition measured with total body electrical conductivity (TOBEC). Finally, we related BMD to energy expenditure and intake.

SUBJECTS AND METHODS

Eumenorrheic Subjects

Twenty-eight white female subjects aged 15 to 21 years participated in this study after giving informed consent in accordance with the procedures established by Baylor College of Medicine (Houston, Tex) and Texas Children's Hospital (Houston) Institutional Review Boards for Human Research. For subjects younger than 18 years, consent was also obtained from parents or guardians. All of the subjects were eumenorrheic, did not smoke, and had no medical problems affecting bone metabolism. Those criteria were established by telephone interview before entering the study. Eumenorrhea was defined as nine to 14 menstrual periods over the past 12 months. Women with fewer than nine or more than 14 menstrual periods per year were excluded. Four women had nine menstrual periods, one had 14, one had 13, and the remainder had 10 to 12 menstrual periods in the previous 12 months. Twenty-three of the 28 subjects had never used estrogen therapy, and five had used oral contraceptives in the past but none during the past 6 months. The subjects were recruited via posters on local university campuses, letters sent to local physicians, a notice run in a university newspaper, and word-of-mouth among the medical staff at Texas Children's Hospital. Fourteen subjects did not exercise regularly, and the other 14 participated on a school team or exercised regularly. The individual activities of those who exercised regularly included jogging/walking (n=4) and dancing (n=1).

Amenorrheic Subjects

Eight subjects with hypothalamic amenorrhea were studied. The serum prolactin level was lower than 0.01 µg/L; follicle-stimulating hormone, less than or equal to 0.01 IU/L; luteinizing hormone, less than or equal to 0.008 IU/L; and thyroid-stimulating hormone, less than or equal to 3.2 mU/L in six subjects. Two subjects with anorexia nervosa did not have these measurements taken as part of their evaluation. Amenorrhea was defined as absent menstrual periods for at least 3 months. Six of the eight females were amenorrheic for at least 12 months, and a seventh subject had one menstrual period in the previous 12 months. The eighth subject was amenorrheic for 3 months at presentation with anorexia nervosa. These eight subjects had been amenorrheic for a mean duration of 15 months. Five subjects were seen in the Eating Disorders Clinic at Texas Children's Hospital and were diagnosed as having anorexia nervosa based

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on *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria.[13] The other three who were not formally evaluated for eating disorders were amenorrheic athletes. One was an Asian Indian gymnast, one was a cross-country runner, and the third was on a drill team and did aerobics regularly. Bone density measurements of all eight patients were taken as part of their clinical assessment.

Protocol

Subjects reported to Women's Health Institute, Houston, Tex, where menstrual history and BMD measurements were taken. Menstrual status was considered a dichotomous variable, with eumenorrheic subjects assigned a value of 0 and amenorrheic subjects a value of 1. Subjects were seen in the Body Composition Laboratory at Texas Children's Hospital for TOBEC measurements, anthropometric measurements, and questionnaire completion, including medical history and an estimate of secondary sexual development.[14,15]

BMD

Bone mineral density of the femoral neck and lumbar spine in the eumenorrheic subjects, and of the lumbar spine only in the amenorrheic subjects was measured using dual energy x-ray absorptiometry (DPX Lunar Radiation Corp, Madison, Wis).[16] The specific techniques for both densitometer measurements have been described previously.[17] Dual energy x-ray absorptiometry scans offer the advantage of less radiation exposure than with older dual photon absorptiometers, the latter using radioactive isotopes as sources of radiation. Bone mineral density was calculated as follows: BMD (g/cm^2) = [Bone Mineral Content (g)]/[Bone Area (cm^2)] with bone area referring to the cross-sectional area of the bone measured. The bone mineral content is a measure of mineralization of bone in grams, with the strength of bone related to its mineralization. The reproducibility of the densitometer used in this study is 2%. The densitometer is calibrated using a phantom of known density every other week, along with a daily calibration check. Radiation exposure is less than 2 mrem per lumbar scan and per femoral neck scan.[16]

Fat-free Mass

Fat-free mass was estimated with TOBEC measurements (model HA2, EM-SCAN, Springfield, Ill).[14] The subject remained fully clothed and lay supine on a motorized carriage. The subject was transported through the electromagnetic coil, during which serial measurements were made and a whole body conductivity value obtained. This was repeated three times and the measurements were averaged. The curve resulting from plotting the individual measurements was subjected to Fourier analysis and fat-free mass was calculated.[18] Measurements taken using TOBEC were precise to within 1.0%.[19]

Anthropometric Measurements

Height and weight were measured at the time of the TOBEC measurement using an electronic scale (Scale Tronix, Wheaton, Ill) and a stadiometer (Holtain Ltd, Crymmych, Pembs, England). Values were rounded to the nearest 0.1 cm and 0.1 kg, respectively. All measurements were taken by one of two trained research assistants. Ideal body weight was calculated using standardized tables.[20,21] Body mass index was calculated as body weight in kilograms divided by height in meters.[2]

Physical Activity

The level of physical activity of the eumenorrheic subjects was assessed with the Minnesota Leisure Time Physical Activity questionnaire.[22,23] The data were reported as estimated kilojoules expended per day in leisure activities over the past 12 months. Leisure activities include physical activities outside school and work, such as recreational or competitive sports, jogging, walking, or dancing.

Table 1.—Descriptive Statistics of 28 Eumenorrheic and Eight Amenorrheic White Women

	Mean ± SD Values (Range)	
Variable	**Eumenorrheic**	**Amenorrheic**
Age, y	18.4 ± 2.2 (15-21)	16 ± 2.1 (14-19)*
Height, cm	163.7 ± 6.6 (148.5-175.3)	161.3 ± 2.3 (158-165)
Weight, kg	57.4 ± 8.1 (42.5-82.2)	44.7 ± 3.6 (39.5-50)*
Percentage of ideal body weight	98 ± 10 (88-135)	83 ± 4.5 (75-90)*
Menarche age, y	12.6 ± 0.9 (11-14)	13.6 ± 1.9 (11-17)
Menses during past 12 mo	11.6 ± 1.3 (9-14)*	1.3 ± 3.5 (0-9)†

*$P<.01$.

†See "Subjects and Methods: Amenorrheic Subjects" for explanation.

Energy Intake

Energy intake for the eumenorrheic subjects was estimated using 24-hour recall and the Nutritionist III software package (N-Squared Computing, Silverton, Ore).

Statistical Analysis

Data were analyzed using Minitab software, version 7.1 (Minitabs Inc, State College, Pa). The BMD data are reported as means and SDs. Pearson correlation coefficients were calculated between BMD measurements and age, weight, height, and fat-free mass. Unpaired *t* tests were used to test for significant differences between the eumenorrheic and amenorrheic subjects with respect to historical, anthropometric, and measurement variables. Simple correlations were used to assess the relationship between BMD and individual variables, including anthropometric measurements and menstrual status. Analysis of covariance was used to assess the effect of weight, menstrual status (0 indicates eumenorrheic, and 1, amenorrheic), and the interactive term *weight* × *menstrual status* on lumbar BMD.

RESULTS

The subjects' age, height, weight, percentage of ideal body weight, and gynecologic history are presented in Table 1. The BMD of the lumbar spine and femoral neck by age for the eumenorrheic subjects are presented in Table 2. Mean (±SD) BMD of the lumbar spine for the eumenorrheic group was 1.213±0.117 g/cm^2, and for the femoral neck was 1.032±0.092 g/cm^2. Lumbar spine BMD was not significantly related to leisure time energy expenditure ($P=.14$). Table 3 presents the correlations between BMD at the lumbar spine and femoral neck and weight, fat-free mass, height, body mass index, and age for the eumenorrheic subjects. Bone mineral density at the two sites was significantly related to weight and fat-free mass for all eumenorrheic subjects combined but not related to age. The correlation between height and femoral BMD (.36) was significant ($P=.06$). The relationship between height and lumbar spine BMD for the eumenorrheic and amenorrheic subjects together, or for the eumenorrheic subjects alone, was not significant ($P=.20$). When the eumenorrheic and amenorrheic subjects were combined, the relationships between lumbar BMD and weight, height, and age were $r=.69$ ($P<.001$), $r=.25$ ($P=.14$), and $r=.11$ ($P=.5$), respectively.

The mean lumbar BMD of the amenorrheic subjects was 1.057±0.113 g/cm^2, which was lower than that of the eumenorrheic subjects ($P=.007$). However, when controlling for weight, the difference was not significant

Table 2.—Lumbar Spine and Femoral Neck Bone Mineral Density by Age in 28 Eumenorrheic White Females Ages 15 to 21 Years

	Age, y				
	15	16-17	18	19	20-21
No. of subjects	5	5	4	7	7
Mean ± SD bone mineral density of L-2 to L-4 g/cm^2*	1.26 ± 0.05	1.20 ± 0.07	1.17 ± 0.03	1.21 ± 0.18	1.22 ± 0.15
Mean ± SD bone mineral density of femoral neck, g/cm^2	1.09 ± 0.11	0.99 ± 0.08	1.00 ± 0.06	1.03 ± 0.10	1.04 ± 0.08

*L-2 indicates the second, and L-4, the fourth lumbar vertebra.

Table 3.—Pearson Correlation Coefficients Between Bone Mineral Density of the Lumbar Spine and Femoral Neck and Weight, Fat-free Mass, Height, and Age for Eumenorrheic Subjects

	L-2 to L-4		Femoral Neck	
Variable	*r*	*P*	*r*	*P*
Weight	.61	.001	.48	.01
Fat-free mass	.57	.002	.51	.006
Height	.25	.20	.36	.06
BMI	.58	.001	.38	.06
Age	−.13	.53	−.14	.49

*L-2 indicates the second, and L-4, the fourth lumbar vertebra.

($P = .35$). The interactive term *weight* × *menstrual status* was not significantly related to lumbar BMD.

The median estimated leisure time energy expenditure of the eumenorrheic subjects was 1478 kJ (range, 172 to 4318 kJ). Femoral neck BMD was significantly related to leisure time energy expenditure ($r = .43$, $P = .02$), but when controlling for weight, this relationship was not statistically significant ($P = .08$). Estimated median daily calorie and median calcium intake for the eumenorrheic subjects were 10143 kJ (range, 3280 to 18278 kJ) and 21.7 mmol (range, 7.9 to 46.4 mmol), respectively. Bone mineral density at both sites was unrelated to estimated calcium intake.

COMMENT

The lumbar BMD values in the amenorrheic subjects were significantly lower than in the eumenorrheic subjects, similar to previous reports.[2,5,6,24-26] Reduced bone density is related to both estrogen and progesterone deficiency.[7,8,27] The exact mechanisms by which estrogens and progesterone increase bone mass is unclear, but the predominant effects of estrogen and progesterone are to limit bone resorption and promote bone formation, respectively.[7] Bone mineral density is expected to improve in females with hypothalamic amenorrhea when treated with combined estrogen and progestin or progestin alone. However, the bone densities of the two groups were not significantly different when controlling for weight. Warren et al[27] reported that the effects of amenorrhea on spine, wrist, and metatarsal BMD were eliminated by controlling for body weight. Warren et al[27] have demonstrated the weight-dependent effects of estradiol on BMD and suggests that the effects of weight-bearing exercise on BMD occur only in a normal estrogen environment. Although the current study was not designed to test this hypothesis, we propose that changes in lumbar BMD in amenorrheic women treated with estrogen/progestin or progestin therapy alone will be minimal unless the subject also gains weight. This could be tested by a prospective, randomized study assessing the effect of estrogen/progestin or medroxyprogesterone acetate therapy on BMD in women with hypothalamic amenorrhea, controlling for weight changes.

The relationships between BMD, weight, and fat-free mass were comparable with those in previous reports.[6] Mazess et al[28] reported a significant relationship between body weight and lumbar BMD ($r = .38$) for 20- to 39-year-old, white, healthy, eumenorrheic women. A 10-kg weight difference was associated with a 3% to 4% difference in BMD at the lumbar spine in their subjects. On the average, the 10-kg weight difference in our subjects corresponded to a 7% difference in lumbar BMD. We are not suggesting that this relationship between body weight and BMD be used to predict BMD changes with weight changes for individuals. Rather, we are stating that, on the average, we noted a difference in BMD between two groups of subjects with different mean weights when examined in a cross-sectional fashion. Bachrach et al[6] reported a significant relationship between lumbar BMD and body mass index ($r = .45$) in eumenorrheic adolescents. In autopsies on adults, Doyle et al[29] reported that the ash weight of the third lumbar vertebra (L-3) was significantly related to the psoas muscle weight ($r = .72$) and the body weight ($r = .47$). When psoas muscle weight was controlled, the correlation between the L-3 ash weight and body weight was not significant, supporting the hypothesis that the mass of the muscle attached to a bone was more closely related to the mass of that bone than total body weight. Cohn et al[30] reported that the higher radial bone density in black women than in white women could be related to the increased muscle mass in black women. As subjects age from preadolescence through puberty, the density of fat-free mass increases, due primarily to increased osseous mineral content and decreased water content of fat-free mass.[31-34] Bone density becomes a progressively larger component of the fat-free mass, then, through puberty. The advantage of measuring fat-free mass by TOBEC is that it does not measure the crystalline portion of bone, and as such, the fat-free mass measurement is not influenced by bone density.

This is the first study that we are aware of that has reported femoral neck BMD measurements done with dual energy x-ray absorptiometry in eumenorrheic white subjects in the 15- to 21-year age group. Previous studies have documented the changes in lumbar BMD in subjects aged 1 to 18 years and older than 20 years.[5,10-12] To our knowledge, there are four previous reports of lumbar spine BMD in eumenorrheic, white subjects in the 15- to 21-year age group,[6,12,35,36] all of which demonstrate that bone accretion peaks in late puberty. Age was not related to BMD at either the lumbar or femoral site in our eumenorrheic subjects. Once pubertal maturation is reached, there may be insignificant increases in BMD of the lumbar spine or femoral neck with age in healthy eumenorrheic females. It may be that aggressive attempts to maximize BMD by middle puberty in girls with hypothalamic amenorrhea should be initiated if there is less potential for bone accretion later in the second decade. However, even though the results of this study suggest that treatment of young adolescents with hypothalamic amenorrhea with sex steroids may be indicated, the current study is cross-sectional and involves a small number of subjects for each age. More information is needed before it can be concluded that the window of opportunity to improve BMD in women with hypothalamic amenorrhea is closed after midpuberty. Alternately, women with prolonged amenorrhea during middle to late puberty may have greater potential to accrete bone mass during the latter half of the second decade than eumenorrheic girls with normal growth and menstrual function.

The physical activity of the eumenorrheic subjects was estimated using the Leisure Time Questionnaire and the results suggest they were representative of high school and college age females. Using the same questionnaire, the leisure time energy expenditure of nonathletic female college students was estimated to be 1381.8±1764 kJ/d and for collegiate female swimmers to be 2620.8±3015.6 kJ/d, including swimming.[22] This is the first study we are aware of that has related an estimate of energy expenditure to BMD and suggests that changes in femoral neck BMD may be more closely related to exercise than lumbar BMD changes in eumenorrheic subjects. Prior et al[8] reported that changes in thoracic and lumbar BMD over 1 year were unrelated to exercise in 20- to 39-year-old white women.

Mazess and Barden[37] reported no relationship between current calcium intake and BMD in 20- to 39-year-old healthy women that is consistent with the findings in this report.

In summary, the difference in lumbar BMD between a group of eumenorrheic white subjects and a group of amenorrheic subjects could be explained by differences in weight, suggesting that the relationship between menstrual status and bone density depends on body weight. The lumbar and femoral BMD in the eumenorrheic subjects peaked in the late pubertal years, suggesting that a crucial time for maximizing lumbar and femoral neck BMD is during midadolescence.

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CORRECTION

Incorrect Data

A number was incorrectly published in the article entitled "Legalization of Drugs of Abuse and the Pediatrician," in the October 1991 issue of *AJDC* (1991;145:1153-1158). On page 1156, under the subhead entitled "No Increase in Drug Use If Drugs Were Legalized," the figure quoted for nationwide use by high school seniors should have been 42%, not 4%. The sentence should have read, "By 1988, use by Alaskan high school seniors remained at 68% compared with the much reduced nationwide figure of 42%."

Retrieval of Placental Blood From the Umbilical Vein to Determine Volume, Sterility, and Presence of Clot Formation

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• From August 1988 to October 1989, 60 specimens of citrate-phosphate-dextrose-adenine anticoagulated blood were retrieved from the placental umbilical veins of newborns from three gestational age groups. The specimens were removed with a needle and syringe apparatus and placed directly into sterile transfusion packs. The specimens were evaluated for the volume obtained, sterility, and presence of macroscopic clots. A blood volume sufficient to provide at least one transfusion (10 mL/kg) for 87% of the premature infants studied was retrieved from the placenta. A greater blood volume per unit of birth weight was recovered from the placentas of the smaller newborns. A 12% positive culture frequency and a 7% frequency of detectable clots were identified. These rates of occurrence suggest the need for further studies to determine the origins of these complicating factors before the adoption of this technique in the clinical setting. These findings support the hypothesis that, with proper patient selection and with specimen culture and filtration, placental blood may be a viable option for the autologous transfusion of sick, premature infants.

(*AJDC*. 1992;146:36-39)

The concern over transmission of infectious agents by homologous transfusion has increased in recent years.[1] Improvements in current neonatal care have led to the need for frequent red blood cell transfusions in premature infants. Review of the medical literature indicates that a majority of neonates born at less than 1500 g receive one or more red blood cell transfusions during hospitalization.[2,3] In 1986, 31% of the neonates admitted to the intensive care unit at Minneapolis (Minn) Children's Medical Center required three or fewer red blood cell transfusions (J.F., unpublished data, 1987).

For editorial comment see p 21.

Previous investigators suggested that it may be feasible to use heparinized placental blood for immediate expansion of the blood volume of a sick neonate.[4-7] They identified concerns relative to appropriate anticoagulation and sterility.[5] Horn et al[8] and Brandes et al[9] have studied storage-induced changes in placental red blood cells. Citrate-phosphate-dextrose-adenine (CPDA-1) was identified as the optimal storage medium for anticoagulated fetal red blood cells. Brandes et al[9] identified the need to study the amount of blood that can be collected from the placenta and the frequency of bacterial contamination of stored placental blood.

This study was designed to determine if placental blood can be withdrawn from the umbilical vein, anticoagulated with CPDA-1, and placed in a standard blood bank storage bag. In addition, we examined the frequency of bacterial contamination, the presence of clotting, and the potential volume obtained from the placenta.

PATIENTS, MATERIALS, AND METHODS

This prospective study was approved by the Institutional Review Board of Abbott Northwestern Hospital, Minneapolis, Minn. Informed consent was obtained from the mother at the time of admission to the labor and delivery department. Subjects were selected on the basis of approval by the parent, the availability of the investigator (S.A. or G.W.), and the gestational age of the newborn. Two mothers declined to participate in the research. Twenty patients were studied from each of the three predetermined gestational age groups: 28 to 32 weeks, 32 to 36 weeks, and 36 weeks to term. All patients were enrolled in the study between August 1988 and October 1989.

Placental Blood Collection Apparatus

Placental blood was collected with a device that incorporated a 19-gauge butterfly needle, two three-way stopcocks (used to store and mix the CPDA-1 with the retrieved placental blood), a 35-mL syringe for withdrawing the blood from the umbilical vein, a 12-mL syringe attached to one of the sideports of the three-way stopcock, and a standard Fenwal 4R2024 Transfer Pack (Baxter Healthcare Corp, Deerfield, Ill). The system was assembled, autoclaved, and stored until use.

Procedure

Immediately after delivery of the newborn and before the delivery of the placenta, the obstetrician cleansed the umbilical cord for at least 10 seconds, using a povidone-iodine scrub. The cord was wiped with isopropyl alcohol and the umbilical vein was pierced with the 19-gauge butterfly needle. Placental blood

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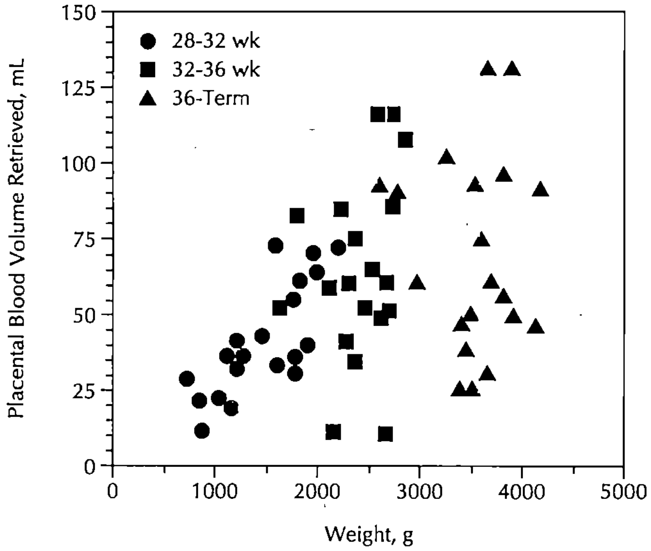
Table 1.—Clinical Characteristics of the Maternal and Neonatal Population (N = 60)*

Gestational Period	Twins, No. (%)	HTN, No. (%)	ABR, No. (%)	Fever, No. (%)	CS, No. (%)	Sex, No. F/M
28-32 wk	4 (20)	6 (30)	3 (15)	2 (10)	11 (55)	9/11
32-36 wk	6 (30)	4 (20)	2 (10)	3 (15)	8 (40)	10/10
36-term	0	6 (30)	0	0	1 (5)	11/9
Total	10 (17)	16 (27)	5 (8)	5 (8)	20 (33)	30/30

*Twins indicates the number of individuals from twin births; HTN, maternal hypertension as defined as blood pressure greater than 140/90 or an increase of the systolic pressure of 30 mm Hg or the diastolic pressure of 15 mm Hg from prenatal or first visit baseline; ABR, placental abruption; Fever, maternal fever as defined by an oral temperature of ≥38.1°C; and CS, cesarean section.



Blood volume vs patient birth weight stratified for gestational age. The equation for the line of linear regression is $y = 25.1 + 0.0133x$ ($R^2 = .185$).

was withdrawn from the vein in 28-mL aliquots to which 3 to 4 mL of CPDA-1 was added. This resulted in a 1:7 to 1:8 dilution consistent with the ratios described by other authors.[3,9] The anticoagulated blood was then transferred from the 35-mL syringe to the attached Fenwal transfer pack. Paired aerobic and anaerobic cultures were immediately obtained. Cultures for *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis,* and herpes simplex virus 2 were not performed. The aliquots were filtered within 24 hours to visually determine the presence of macroscopic clots.

For bacterial culture, 3 to 5 mL of the placental blood was aseptically removed from the transfer pack and injected into culture bottles (Bactec, Johnston Laboratories, Sparks, Md). The blood cultures were monitored on an automated blood culture instrument that measures generation of carbon dioxide by the microorganism for 7 days.

Filtering

The blood remaining in the transfer pack was primed through standard Fenwal transfusion tubing and filtered using the Fenwal PDF-20 pediatric transfusion filter set. The intact filter was inspected for gross clots by the blood bank technician.

Statistical Analysis

Differences between variables were analyzed using a two-tailed *t* test for independent samples and χ^2 analysis (SPSS Inc, Chicago, Ill). Differences were considered significant at $\alpha < .05$.

RESULTS

Table 1 shows the clinical characteristics of our patient population. Sixty newborns (30 female and 30 male) were studied. There were five sets of twins, all in the premature gestational age groups.

Table 2.—Placental Blood Volume Stratified by Volume Recovered and Compared With Birth Weight

Stratified Blood Volume mL/kg*	Mean Birth Weight, g	Mean Blood Volume, mL	Mean Blood Volume, mL/kg	No.†
0-10	3085	20.0	6.2	8
10-20	2834	42.0	15.3	20
20-30	2416	55.8	23.0	19
30-40	2247	75.2	33.3	9
>40	1879	83.4	44.0	4

*Blood volume retrieved from the placenta is statified in aliquots of 10 mL/kg, the usual volume used for neonatal transfusion.

†Number of specimens per stratified blood volume when 6 mL of wastage volume is substracted from the total volume retrieved.

Maternal hypertension was evenly distributed throughout the three gestational age groups ($P = .68$ by χ^2). Only five of the mothers (8%) were febrile. Cesarean section deliveries comprised 20 of the total deliveries (33%); however, the majority of cesarean deliveries occurred in the premature gestational age groups. There was no statistically significant difference between the frequencies of positive bacterial cultures in cesarian section and vaginal delivery groups ($P = .97$ by χ^2). The blood volume plotted against the birth weight shows a linear association ($R^2 = .115$) and an inverse relationship with the smaller newborns, providing a greater placental blood volume per kilogram of birth weight (Figure). There was substantial variability in the volume retrieved compared with weight. More blood was retrieved from the female patients (66 mL/kg) than the male patients (50 mL/kg, $P = .03$). There is no apparent explanation for this finding.

The data are stratified into 10-mL/kg ranges because neonatal red blood cell transfusions are usually administered in aliquots of this volume (Table 2). Mean birth weight and mean blood volume were calculated for each stratification. Eighty-seven percent of the specimens (52 of 60) provided enough blood for at least one 10-mL/kg transfusion and 53% (32 of 60) provided enough for two or more transfusions. These calculations take into account a wastage volume of 6 mL for the transfusion tubing.

Twelve percent of the specimens (seven of 58) were positive for bacterial contamination. Three of the cultures yielded group B β-hemolytic *Streptococcus.* Two of the three newborns who tested positive for group B *Streptococcus* in the placental sample either had a positive blood culture in the neonatal intensive care unit or associated risk factors that made it likely that the placental culture was a true-positive indicator for the presence of bacteremia.

The third newborn who tested positive for group B *Streptococcus* was delivered vaginally. The mother had a positive vaginal culture for group B *Streptococcus*, and multiple punctures of the umbilical vein were required to obtain the specimen.

Common vaginal flora were cultured from the four remaining contaminated specimens. Review of the collection technique indicated that these were probably due to a breakdown in the integrity of the sterilized system. Problems included disconnection of the tubing during withdrawal of the placental blood and multiple punctures of the umbilical vein.

Visible clots were noted in 7% of the specimens (four of 56). Four specimens had insufficient volume after culturing to evaluate for clots. No significant study variables were associated with the presence of visible clotting.

When all factors are considered (volume, culture, and clots), 77% of the samples (46 of 60) were appropriate for autologous transfusion.

COMMENT

The number of autologous transfusions and autologous donations for elective surgery has increased in the past 6 years.[1] Cardiovascular and orthopedic surgeons have instituted new methods to decrease the risk associated with exposure to homologous blood.[10-14] These efforts include the use of predeposited autologous blood and sophisticated techniques for the retrieval and processing of autologous blood from the operative wound. The use of autologous blood for transfusion during the third trimester of pregnancy appears to be safe and has been strongly encouraged for patients with placenta previa.[15,16]

The preterm newborn may benefit from autologous transfusions. Hospitalized preterm infants undergo significant blood loss from the blood sampling needed for their care.[17,18] The frequent use of red blood cell transfusions in the neonatal intensive care unit has led to an increased interest in identifying the indications for and the risk factors associated with homologous transfusions.[2,3]

Fetal hemoglobin plays an important physiologic role in the fetus. At any given Po_2, fetal hemoglobin carries 20% to 30% more oxygen than does adult hemoglobin.[19] In the sick, premature infant with suboptimal respiration and alveolar diffusion, the alveolar Po_2 is less than that found in the normal respiring infant. Several authors refer to an arterial Po_2 (crossover Po_2) below which shifts to the right in the oxygen dissociation curve are no longer advantageous to the neonate.[20-22] This crossover Po_2 is important when the venous Po_2 is low. In this situation, the Po_2 delivery by fetal hemoglobin is better than that by adult hemoglobin when the cerebral venous Po_2 is approximately 10 mm Hg and the arterial Po_2 is less than 53 mm Hg.[21] Further shifting of the dissociation curve to the right through the effects of pH and Pco_2 may also accentuate the efficacy of fetal hemoglobin in the sick neonate. The use of fetal hemoglobin for transfusions may offer opportunities to compare the effects of fetal vs adult hemoglobin in the clinical setting.

The use of placental blood for autologous transfusion may be an alternative to homologous transfusion if adequate collection and storage techniques can be developed. Brandes et al studied placental blood using citrate-phosphate-dextrose and compared it with adult blood for adenosine triphosphate and 2,3-diphosphoglyceric acid concentrations. The adenosine triphosphate concentrations did not fall below the normal range for adult erythrocytes during the 8 days the samples were studied.[9] The 2,3-diphosphoglyceric acid concentrations decreased below the normal range for fresh adult erythrocytes by day 3. Horn et al[8] used the improved medium CPDA-1 and showed increased adenosine triphosphate and 2,3-diphosphoglyceric acid concentrations compared with those cells stored in citrate-phosphate-dextrose. The clinical significance of this is unclear because 2,3-diphosphoglyceric acid concentrations return to normal within 24 hours of transfusion.[23] Both studies conclude that fetal red blood cells could be a suitable red blood cell source to transfuse neonates.[8,9]

The present study demonstrates that the placenta is capable of providing an adequate volume of blood for autologous transfusion. This volume is sufficient to provide at least one transfusion (10 mL/kg) for 87% of the newborns studied. The ramification of this finding is important for our neonatal intensive care unit, where 63% of all neonates weighing less than 2000 g required at least one red blood cell transfusion during 1989.

The frequency of placental blood specimens contaminated with bacteria in this study is consistent with that reported by Golden et al.[4] In the study by Golden et al, the overall positive rate of 9.7% included several organisms similar to our own (*Staphylococcus epidermidis* and *Lactobacillus* species). These rates are much higher than the rate of bacterial contamination present in banked homologous blood.[24] The argument to eliminate the risk of exposure to infectious agents (human immunodeficiency virus and cytomegalovirus) in homologous blood must be balanced against the risk of bacterial contamination that may occur in the harvesting of placental blood. Before autologous placental blood can be routinely used, several questions need to be answered. These include the definite procedures for cleansing of the umbilical cord, withdrawal of placental blood, and routine culture and storage of the specimen.

The organisms isolated in this study are probably contaminants and secondary to either poor technique, contamination from inflamed umbilical cords, or true-positive cultures from the umbilical vein. Group B *Streptococcus* was isolated in two cases and was associated with maternal infection and positive blood cultures in the patient or the twin sibling. It appears that a subpopulation of premature infants and their mothers are at high risk for bacteremia, and should not be included in the potential group to benefit from autologous placental transfusion. Improvements in technique, further identification of at-risk mothers, and cultures of the specimen should decrease the number of contaminated placental blood specimens.

Homologous blood transfusions, particularly from first-degree relatives, may expose the recipient to the risk of alloimmunization and graft-vs-host disease.[25,26] This has prompted the American Association of Blood Banks to recommend that all cellular blood products from first-degree relative be irradiated before transfusion.[26] Autologous placental blood transfusions contaminated with maternal blood may also expose the recipient to the risk of alloimmunization and graft-vs-host disease. Further study is required to identify the frequency of maternal blood contamination in autologous placental blood.

No significant association with the presence of clots and other risk factors in the delivery of premature infants was observed. Because of the routine use of filters in the administration of red blood cells to sick neonates, the infrequent presence of clots in our study does not appear to be a significant factor.

In spite of recommendations not to depart from the standard blood banking practices for neonatal transfusion, options exist to provide blood from donors chosen by the family or the physician (directed donors).[25,27-31]

In most cases, the arterial Po_2 in sick, premature infants is best maintained with adult hemoglobin when transfusions are indicated.

Autologous fetal hemoglobin transfusions may "bridge" the time between the birth of the infant and the establishment of an appropriate directed donor.

Finally, the concern regarding risks of receiving homologous transfusions must be recognized. We believe that further study on the use of autologous placental blood is warranted and that it may be a reasonable and appropriate addition to the list of options available to supply red blood cell transfusions to the sick, premature infant.

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Very Low Birth Weight and Growth to Age 8 Years

I: Weight and Height

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• We determined the heights and weights at ages 2, 5, and 8 years for the following three cohorts of children: group 1 with birth weights between 500 and 999 g; group 2 with birth weights between 1000 and 1499 g; and group 3 with birth weights more than 2500 g. By age 8 years, group 3 children were significantly heavier and taller than all children in groups 1 and 2 combined; group 1 children were significantly shorter than those in group 2, but their weights were similar. From ages 2 to 5 years, annual increments in weight and height were similar in all three groups; however, between ages 5 and 8 years, children in group 3 grew faster than those in groups 1 and 2 combined, and children in group 1 had smaller height increments than those in group 2. Of children with birth weights less than 1500 g, with a weight or height under the 10th percentile at age 2 years, only approximately one half were still below the 10th percentile for the corresponding measurement at age 8 years. Health variables determined before birth, such as maternal height or birth weight ratio, were more important than health after birth in predicting a height or weight below the 10th percentile at age 8 years in children with birth weights less than 1500 g.

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Reports from several countries indicate that children with very low birth weight (VLBW, birth weight less than 1500 g) often grow poorly in early childhood.[1-8] This problem is even more prevalent in children with extremely low birth weight (ELBW, birth weight less than 1000 g).[6,8-12] Until synthetic growth hormone became widely available, short stature in these children was usually a matter of academic rather than practical interest. Children with VLBWs, especially ELBWs, of short stature are an obvious group for a trial of synthetic growth hormone; however, data are limited on their height after early childhood, particularly for ELBW children born in the era of modern neonatal intensive care. Their adult stature is uncertain.

See also p 46.

In an earlier report, we were unable to find convincing evidence of catch-up growth between ages 2 and 5 years in a cohort of 135 children with birth weight under 1501 g.[12] However, only 28 children had ELBW, and the time span of 3 years was relatively short. We therefore reassessed the growth of all available children in our longitudinal studies who had reached age 8 years, including a group of children with normal birth weight (birth weight more than 2500 g). We identified the following three groups of children: group 1 consisted of children with birth weight between 500 and 999 g; group 2 consisted of children with birth weight between 1000 and 1499 g; and group 3 consisted of children with birth weight more than 2500 g.

The aims of the study were: (1) to contrast the height and weight achieved by age 8 years between the three birth-weight groups; (2) to contrast the growth rates between ages 2, 5, and 8 years between the three groups; (3) to seek evidence of catch-up growth of those VLBW children who were underweight or of small stature at age 2 years; and (4) to determine whether prenatal or postnatal variables were more important in predicting height or weight below the 10th percentile at age 8 years in VLBW children.

PATIENTS AND METHODS

The children in this report comprised two cohorts of preterm infants and a normal-birth-weight comparison group. Group 1 comprised 79 consecutive children with birth weight between 500 and 999 g born between January 1, 1977, and March 31, 1982. Group 2 included 111 consecutive children with birth weight between 1000 and 1499 g born between October 1, 1980, and March 31, 1982. Group 3 comprised 56 randomly selected children with birth weight over 2500 g born during the same period as the group 2 children.

In the original cohorts from which these children were derived, there were 85 children with birth weights less than 1000 g, 124 with birth weights between 1000 and 1500 g, and 60 with birth weights more than 2500 g. For the present study, three groups of children were excluded from the original cohorts: eight nonwhite children; 11 children with moderate or severe physical disability from cerebral palsy; and to conform with the con-

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vention of 1499 g as the upper limit of VLBW, four children with birth weight exactly 1500 g.

All children were born in the Royal Women's Hospital, Melbourne, Australia, a tertiary center with approximately 6000 births annually from 1977 to 1982; many mothers were at low risk, but the hospital was also a referral center for patients with complications of pregnancy who had been booked elsewhere for delivery. The population included families from a wide socioeconomic spectrum, with social class being based on the occupation of the principal income earner. Mothers were designated as immigrants if they were from a country in which English was not the first language. The duration of the mother's schooling was divided into less than 10 years or 10 years or more. Some families paid fees.

All available children in groups 1, 2, and 3 were assessed on three occasions, as close as possible to ages 2, 5, and 8 years, corrected for prematurity. Weight and standing height were measured in a standardized fashion[13,14]; data on a few children living out of the state of Victoria were obtained from other professional sources. The number and duration of hospital readmissions and illnesses were confirmed with the relevant hospital or medical practitioner. Hospital readmissions were classified according to whether the primary diagnosis was medical or surgical. The percentiles for weight and height originally had been coded using Australian reference data obtained in the early 1970s on a multiracial urban community.[15,16]

The percentiles were then recoded using the National Center for Health Statistics reference values[17] now recommended by the World Health Organization for international comparison.[18] The reference values for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were entered into a computer, and the weight and height of each child was computed into one of the eight possible percentile channels (lower than the 5th, 5th to 10th, etc). Continuous variables for weight and height suitable for multivariate analyses were computed; ratios of weight and height for age were calculated by dividing the observed growth measurement of each child by the 50th percentile reference value listed by the National Center for Health Statistics. These ratios are frequently used in nutritional studies.[19] Similarly, for each child, the ratio of observed birth weight to the 50th percentile for the child's gestational age obtained from reference data applicable to our hospital population in the 1970s[20] was computed.[21] The ratio of length at birth to the 50th percentile was not computed, since length at birth was not measured for all infants. For children with data available at each age, average annual increments in weight and height were computed during the 3-year intervals between 2 and 5 years and 5 and 8 years. Because the intervals between assessments were often not exactly 3 years, the average annual growth increments were calculated by dividing the increase in height or weight between assessments by the exact interval between the measurements.

The height and weight ratios achieved by age 8 years and the annual growth increments between ages 2 and 5 years and ages 5 and 8 years were compared between the three groups using analysis of variance, adjusting for gender when appropriate. For each analysis of variance, linear contrasts were used, first to compare the normal-birth-weight children (group 3) with all VLBW children (groups 1 and 2), and if this difference was significant, to compare ELBW children (group 1) with larger VLBW children (group 2).

Of particular interest to the clinician is the outcome of the shortest and lightest children, particularly those below the 10th percentile. Children with birth weight less than 1500 g at age 2 years were divided into four groups: below the 5th percentile, between the 5th and 10th percentiles, between the 10th and 25th percentiles, and 25th percentile and above; and their values were compared with those at ages 5 and 8 years.

To determine the variables that might predict whether a VLBW child would be below the 10th percentile for weight or height at age 8 years, the data were analyzed with logistic regression. The independent variables studied in chronologic order were sociodemographic factors (social class, mother's duration of schooling, immigrant status, and maternal height), perinatal factors (gestational age, birth-weight ratio, gender, multiple pregnancy, antenatal steroids, parenteral alimentation, duration of ventilation, and bronchopulmonary dysplasia), health from discharge to age 8 years (asthma or recurrent lower respiratory tract infections at age 8 years, and the requirement for hospital readmissions for predominantly medical or surgical indications from discharge to age 2 years, from age 2 to 5 years, and from age 5 to 8 years).

Data were analyzed with a computer using Statistical Package for the Social Sciences-X (SPSS-X) programs.[22] In addition to the statistical tests already mentioned, comparison of categorical variables was done with χ^2 analysis or Fisher's Exact Test, and continuous variables, with Mann-Whitney U test. A value of $P<.05$ on any test was regarded as statistically significant.

RESULTS

No child in any weight group had signs of early puberty, none had a recognized syndrome associated with poor growth, and none have so far been treated with growth-promoting hormones. Growth data at age 8 years were available for 77 (97%) of 79 children in group 1, 100 (90%) of 111 children in group 2, and 50 (89%) of 56 children in group 3. Of the children with no 8-year growth data, none in group 1, three in group 2, and two in group 3 had not been seen on at least one previous occasion.

Sociodemographic and perinatal data of the cohorts are listed in Table 1. The only sociodemographic variable significantly different between the three groups was the higher proportion of immigrant mothers in group 3 than in groups 1 and 2 combined. Children in group 3 differed significantly from those in groups 1 and 2 combined on many perinatal variables, reflecting their better health in the perinatal period. Compared with group 2 children, those in group 1 required longer durations of assisted ventilation and received more parental alimentation; more children of group 1 also developed bronchopulmonary dysplasia and retinopathy of prematurity.

Weight and Height at Age 8 Years

Figures 1 and 2 show the cumulative percentiles achieved for weight and height for children at age 8 years; weight and height percentiles achieved by age 8 years were progressively lower at the lower birth weights.

Weight and height ratios at age 8 years were not significantly different for boys or girls. Children in group 3 (normal birth weight) had a mean (±SD) weight ratio of 1.15±0.23 and a mean (±SD) height ratio of 1.02±0.04 at age 8 years; on average they were significantly heavier by 4 kg ($P<.0001$) and taller by 4 cm ($P<.0001$) than all the children of groups 1 and 2 combined (mean weight ratio, 0.99±0.21; mean height ratio, 0.99±0.05). For children with birth weight less than 1500 g, children in group 1 were significantly shorter by 2.5 cm on average ($P=.001$) than those in group 2 (mean height ratios at age 8 years: group 1, 0.98±0.05; group 2, 1.00±0.05). However, although group 1 children were on average 1.7 kg lighter than those in group 2, their mean weight ratios were not significantly different (group 1, 0.95±0.22; group 2, 1.02±0.19).

For children with birth weight lower than the 10th percentile, nine (69%) of 13 children in group 1, two (33%) of six children in group 2, and none of two children in group 3 were still below the 10th percentile for weight at age 8 years.

Table 1.—Biographical Data on Children Surviving to Age 8 Years

	Group		
	1 (n=79)	2 (n=111)	3 (n=56)
Birth weight range, g	500-999	1000-1499	>2500
Median (10th-90th percentiles)			
Birth weight, g	880 (730-970)	1270 (1050-1460)	3420 (2941-4112)
Gestational age, wk	27 (25-32)	30 (28-32)	40 (38-41)
Age at presentation, mo	98 (95-105)	97 (96-99)	96 (96-97)
Sociodemographic data, No. (%) of patients			
Social class			
Professional/managerial	9 (11)	10 (9)	11 (20)
Skilled/semiskilled	46 (58)	64 (58)	18 (32)
Unskilled/social security	24 (30)	36 (32)	26 (46)
No data	. . .	1 (1)	1 (2)
Maternal education, y			
<10	29 (37)	36 (32)	21 (38)
≥10	49 (62)	70 (63)	28 (50)
No data	1 (1)	5 (5)	7 (12)
Immigrants	21 (27)	21 (19)	23 (41)*
Fee-paying families	36 (46)	39 (35)	26 (46)
Perinatal data, No. (%) of patients			
Antenatal steroid therapy	40 (51)	54 (49)	0 (0)*
Boys	38 (48)	61 (55)	31 (55)
Multiple births	16 (20)	19 (17)	0 (0)*
<10th percentile birth weight	13 (16)	6 (5)	2 (4)
Seizures	3 (4)	4 (4)	0 (0)
Cerebroventricular hemorrhage	9/43 (21)	24 (22)	0 (0)†
Bronchopulmonary dysplasia	38 (48)	6 (5)‡	0 (0)*
Parenteral alimentation	42 (53)	11 (10)‡	0 (0)*
Retinopathy of prematurity	30 (38)	9 (8)‡	0 (0)*
Necrotizing enterocolitis	3 (4)	5 (5)	0 (0)
Duration of assisted ventilation, d			
Median	5	0‡	0§
10th-90th percentiles	(0-40)	(0-8)	. . .

*Statistically significant difference between group 3 and groups 1 and 2 combined.

†No children in group 3 scanned.

‡Statistically significant difference between groups 1 and 2.

§No children in group 3 were ventilated.

Incremental Growth From Ages 2 to 8 Years

The average annual increments in weight and height for the three groups in the two age spans (from ages 2 to 5 years and ages 5 to 8 years) are shown in Table 2. From ages 2 to 5 years, increments in weight and height were significantly greater in girls but were not substantially different between the three groups. Between ages 5 and 8 years, however, growth rates were not significantly related to gender, but children in group 3 grew at higher rates than those in groups 1 and 2 combined. For children with birth weight less than 1500 g between ages 5 and 8 years, those in group 1 had significantly smaller height increments, but not weight increments, than those in group 2.

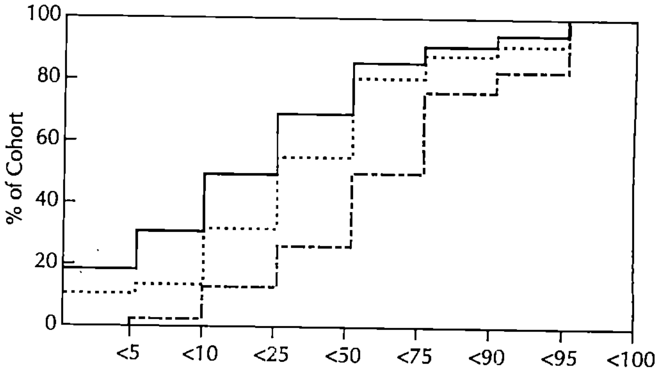

Fig 1.—*Cumulative probability distributions for weight at age 8 years for group 1 (solid line), group 2 (dotted line), and group 3 (dashed line).*

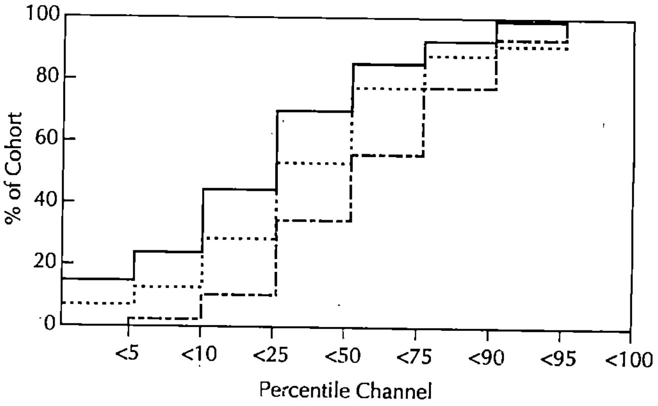

Fig 2.—*Cumulative probability distributions for height at age 8 years for group 1 (solid line), group 2 (dotted line), and group 3 (dashed line).*

Outcome for Short and Light VLBW Children at Age 2 Years

For children with birth weight under 1500 g, the percentiles achieved at age 2 years were compared with those at ages 5 and 8 years (Figs 3 and 4). Of the 165 VLBW children with data at each age, 44 (27%) were below the 10th percentile for weight, and 56 (34%) were below the 10th percentile for height at age 2 years. By age 5 years, 34 (77%) of 44 children remained below the 10th percentile for weight and 33 (59%) of 56 children remained below the 10 percentile for height; by age 8 years, 23 (52%) of 44 children were below the 10 percentile for weight and 23 (41%) of 56 children were below the 10th percentile for height. Children of extremely short stature at age 2 years with heights below the 5th percentile are of particular interest; of 42 children, 19 (45%) and 12 (29%) remained below the 5th percentile at ages 5 and 8 years, respectively. Children remaining below the 5th percentile for height at ages 5 and 8 years were joined by three others at each age who had been above the 5th percentile at age 2 years (one child had been above the 25th percentile at age 2 years).

Table 2.—Average Annual Incremental Weight and Height Gains for Extremely Low-Birth-Weight, Larger Very-Low-Birth-Weight, and Normal-Birth-Weight Cohorts (No Data Missing From Any Age Group)

	Group		
	1 (n=72)	2 (n=93)	3 (n=37)
Birth weight range, g	500-999	1000-1499	>2500
Average annual increment, median (10th-90th percentiles)			
Weight, kg/y			
2 to 5 y	1.80 (1.35-2.73)	1.96 (1.33-2.95)	2.11 (1.63-3.35)
5 to 8 y	2.14 (1.53-3.64)	2.34 (1.71-3.94)	3.05 (1.90-5.08)*
Height, cm/y			
2 to 5 y	7.46 (6.26-8.61)	7.46 (6.56-8.65)	7.59 (6.54-8.92)
5 to 8 y	5.65 (4.64-6.86)	6.10 (5.31-7.19)†	6.37 (5.33-7.21)*

*For group 3 compared with groups 1 and 2 combined, $P<.002$.
†For group 1 compared with group 2, $P<.001$. No other differences were statistically significant.

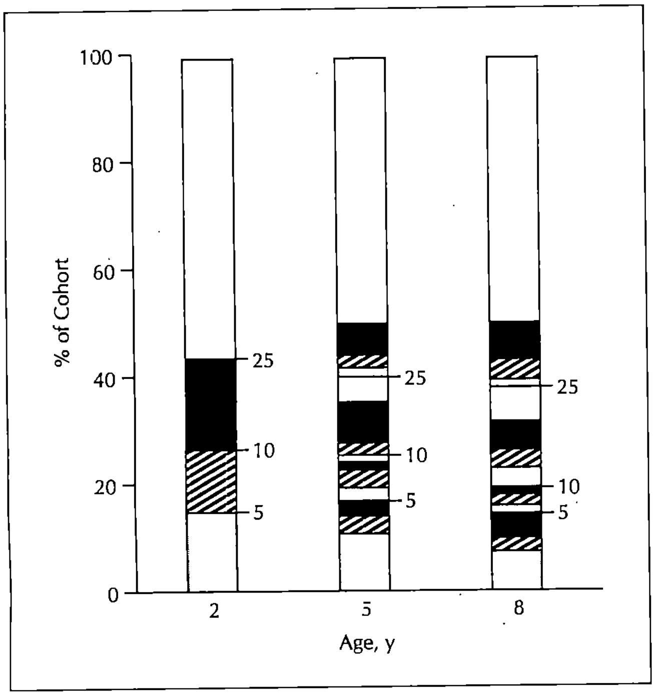

Fig 3.—*Weight distribution at ages 2, 5, and 8 years for 165 children with birth weight less than 1500 g with data at all ages. Numbers adjacent to bars indicate the 5th, 10th, and 25th percentiles at each age. Open bars represent weight above the 25th percentile at age 2 years; closed bars, between the 10th and 25th percentiles; hatched bars, between the 5th and 10th percentiles; and shaded bars, lower than the 5th percentile.*

Prediction of Height or Weight Below the 10th Percentile at Age 8 Years

For children of birth weight less than 1500 g, the only variable significantly associated with a weight below the 10th percentile at age 8 years was a lower birth-weight ratio ($P<.001$). No other sociodemographic, perinatal, or health variables up to age 8 years were statistically significant. The only variable significantly associated with a height below the 10th percentile at age 8 years was a lower maternal height ($P<.001$).

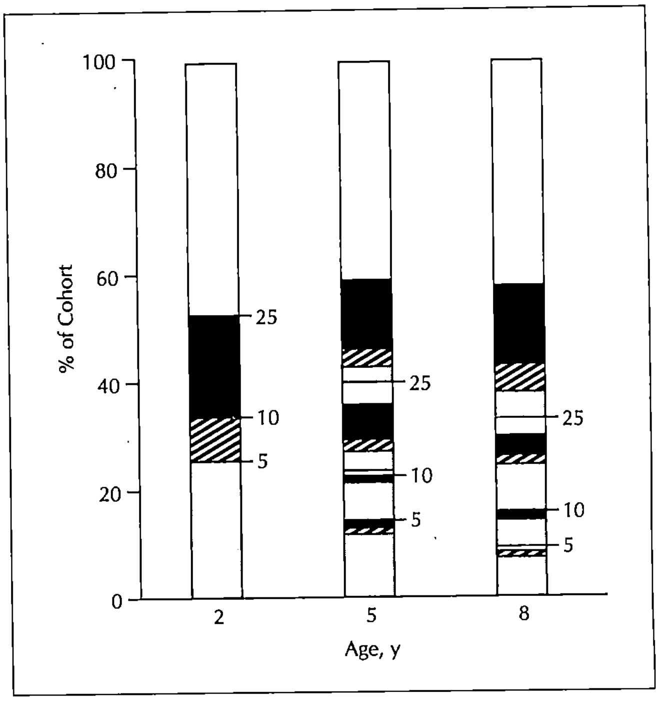

Fig 4.—*Height distribution at ages 2, 5, and 8 years for 165 children with birth weight less than 1500 g with data at all ages. Numbers adjacent to bars indicate the 5th, 10th, and 25th percentiles at each age. Open bars represent height above the 25th percentile at age 2 years; closed bars, between the 10th and 25th percentiles; hatched bars, between the 5th and 10th percentiles; and shaded bars, lower than the 5th percentile.*

COMMENT

Children with moderate or severe cerebral palsy were excluded because measurement of growth, particularly height, may be inaccurate in these children. We excluded children with Asian mothers from the analyses because reference standards based on white children are not appropriate.[14] The debate on which reference values to use continues, with a strong inclination toward using the standards given by the National Center for Health Statistics because of their value for international comparisons[14,18,23]; the World Health Organization stressed that these international standards do not represent the ideal or "gold standard" and that they need to be supplemented with reliable contemporary local data to establish what is normal in a particular community.[18] Consequently, although we compared our VLBW children with our normal-birth-weight children, their ranking on National Center for Health Statistics percentiles was also reported for international comparison.

Apart from differences attributable to more ill health in the perinatal period (antenatal steroid therapy, bronchopulmonary dysplasia, parenteral alimentation, retinopathy of prematurity, and duration of assisted ventilation), group 3 children were significantly different from the VLBW children in two other ways: more group 3 children were born to immigrant mothers and none were from multiple pregnancies (Table 1). The mothers of children in the VLBW cohort were typical of the Australian population as a whole, with 20% to 25% being from countries in which English was not the major language. Being a large urban hospital, the Royal Women's Hospital attracts more women in the immigrant category for normal deliveries; hence the higher proportion in the randomly selected normal-birth-weight group (group 3). The only immigrants excluded from our study were Asians, for reasons given previously. Both immigrant mothers and multiple pregnancies were not large influences on growth in our study, and neither was significantly associated with growth failure at age 8 years. Consequently, we did not exclude children from multiple pregnancies or born to immigrant mothers.

In our study, VLBW children were significantly shorter and lighter at age 8 years than the normal-birth-weight children, observations consistent with our previous report on a smaller cohort of VLBW children at ages 2 and 5 years.[12] Between ages 2 and 5 years, growth rates for normal-birth-weight and VLBW children in the present study were not significantly different, but between ages 5 and 8 years, the VLBW children grew at significantly lower rates than did the normal-birth-weight children. These observations suggest that VLBW children as a group not only do not catch up to their normal-birth-weight peers by age 8 years, but also may fall further behind between ages 5 and 8 years. However, there are individual exceptions to the average, helping to explain why more short and light VLBW children at age 2 years outgrew those categories by age 8 years.

Within the VLBW cohort, group 1 (ELBW) children were significantly shorter at age 8 years than group 2 (larger VLBW) children, but the weight ratios were not significantly different. Growth rates between ages 2 and 5 years were not different between groups 1 and 2, but between ages 5 and 8 years, group 1 children had significantly smaller height increments, which would have contributed to them being significantly shorter at age 8 years. Therefore within the VLBW cohort, group 1 children were more disadvantaged in height than group 2 children, and their increments in height were less.

For the clinician interested in treating short VLBW children with synthetic growth hormone, if the proportions below the 5th and 10th percentiles for height at age 2 years are followed longitudinally, by age 8 years few remain in the shortest categories. Obviously, age 2 years would be too early to embark on growth hormone therapy for *most* short VLBW children; even age 5 years may be too early. The shortest VLBW children (below the 10th percentile) at age 8 years were offered an appointment for evaluation at an endocrine clinic; not all parents accepted this invitation because they or the child were not concerned. We do not have any data on psychological problems specifically related to short stature in our children.

Not all variables in Table 1 were included in the logistic regression analyses. Cerebroventricular hemorrhage was excluded because not all children were scanned in the newborn period (none of group 3 and almost half of group 1). Seizures and nectrotizing enterocolitis were not included because they occurred so infrequently. It was notable that no health variables determined after birth, during the neonatal period or subsequently, were associated with a height or weight below the 10th percentile at age 8 years in VLBW children. Similarly, social variables were not associated with poor growth at age 8 years, a finding consistent with that of Carmichael et al[24] in a recent study of growth to age 4 years in a socioeconomically poor urban Australian community. Not surprisingly, a lower birth-weight ratio was associated with a weight below the 10th percentile at age 8 years, and a lower maternal height was associated with a height below the 10th percentile, indicating that variables originating before birth are stronger determinants of growth failure in childhood than any subsequent ill health after birth.

Because VLBW children are not catching up to their normal-birth-weight peers by age 8 years, and because ELBW children are growing more slowly between ages 5 and 8 years, we will continue to follow up the growth of these children, into adulthood.

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Birds

Western pediatricians may find it difficult to believe that child death is an ordinary, expected, and routine event in many parts of the world. A recent review, "Social Indifference to Child Death," describes poignantly the death of a 3-year-old girl due to malnutrition, recurrent diarrhea, and vomiting. Her mother said, "Infants are like birds, here today, gone tomorrow. Alive or dead, it's all the same to them." The child was dressed in her white, holy communion dress and covered with white flowers before her funeral. On returning to visit the grave some time after the burial, the area had been cleared and the space given to twin infants. The 3-year-old girl's remains had been tossed into the deep well called the bone depository.

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Very Low Birth Weight and Growth to Age 8 Years

II: Head Dimensions and Intelligence

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• The occipitofrontal circumference was measured in all available children in the following cohorts at ages 2, 5, and 8 years: group 1, consisting of 79 children with birth weight between 500 and 999 g; group 2, with 111 children with birth weight between 1000 and 1499 g; and group 3 with 56 children with birth weight greater than 2500 g; all were white with no signs of moderate or severe cerebral palsy. National Center for Health Statistics reference values indicated substantially more children with an occipitofrontal circumference lower than the 10th percentile, particularly at age 2 years, compared with Nellhaus reference data. Occipitofrontal circumference was the head measurement best correlated with the Full Scale IQ on the Wechsler Intelligence Scale for Children–Revised. Dolichocephaly, often seen in very-low-birth-weight children was unrelated to IQ, and correction of occipitofrontal circumference for dolichocephaly was rarely of clinical importance.

(*AJDC.* 1992;146:46-50)

In early childhood, many children with very low birth weight (VLBW; birth weight under 1500 g) grow poorly in height and weight[1-5]; this tendency is even more prevalent in children with extremely low birth weight (ELBW; birth weight under 1000 g).[6-8] In contrast, head growth, as assessed by measuring the occipitofrontal circumference (OFC), is reported as being either less affected or normal.[2,4-9] Normal head growth in ELBW and VLBW children is regarded as reassurance that the brain has been preferentially spared both during primary hospitalization and subsequently during the frequent illnesses to which these children are prone.[10]

See also p 40.

Head circumference is related to infant development[9,11] and later intelligence in childhood,[5,12] and is a useful indication of brain size.[13] However, it is possible that other head measurements, such as cross-sectional area, or anteroposterior (AP) or biparietal (BP) diameters, may be related more strongly to intelligence, and some may not be influenced as much as OFC by dolichocephaly. We recently reported an apparent deterioration in OFC between ages 2 and 5 years in a group of 154 VLBW children and postulated that normalization of their dolichocephalic head shape was the explanation.[8] Using the reference standard of Nellhaus,[14] the children were followed up only to age 5 years and only 28 children had ELBW. Recently, Roche et al[15] have shown that the Nellhaus standards were lower than those of the National Center for Health Statistics (NCHS).[15]

We reviewed aspects of head growth and their relationship to psychological test results of 190 children with birth weight less than 1500 g in our follow-up program who had reached at least age 8 years; results were compared with a group of normal-birth-weight (over 2500 g) children. The aims of the study were: (1) to investigate differences in OFC percentile distribution using the two commonly used reference standards; (2) to determine head growth achieved by age 8 years in cohorts of ELBW and VLBW children and a normal-birth-weight comparison group; (3) to investigate whether correction of OFC for the extremely dolichocephalic skull was of clinical importance at age 8 years; and (4) to determine if head measurements other than OFC were more strongly correlated with intelligence.

PATIENTS AND METHODS

Biographical features of the groups have been described previously.[16] The three groups consisted of white children, with no signs of moderate or severe cerebral palsy, surviving to age 8 years. Group 1 included 79 children with birth weight between 500 and 999 g born between January 1, 1977, and March 31, 1982. Group 2 was composed of 111 children with birth weight between 1000 and 1499 g born between October 1, 1980, and March 31, 1982. The children in groups 1 and 2 were typical of survivors in that age group; many had been quite ill in the newborn period, requiring assisted ventilation, or having had complications such as cerebroventricular hemorrhage, bronchopulmonary dysplasia, and retinopathy of prematurity.[16] Group 3 was composed of 56 randomly selected children with birth weight over 2500 g born during the same period as group 2 children; all group 3 children had been quite healthy in the newborn period. Mothers were designated as immigrants if they were

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Reprints not available.

born in a country where English was not the first language. Social class of families was classified by the occupation of the principal income earner into the following two groups: professional/managerial/skilled/semiskilled and unskilled/receiving social security benefits. The duration of the mother's schooling was divided into less than 10 years or 10 years or more. Children in all the study groups had been delivered at the Royal Women's Hospital, Melbourne, Australia, a large tertiary maternity center.

All available children in groups 1, 2, and 3 were reviewed on three occasions, as close as possible to ages 2, 5, and 8 years, corrected for premature delivery. The psychological assessment included the Wechsler Intelligence Scale for Children–Revised (WISC-R) administered at age 8 years.[17] At each of the three ages, the OFC was measured in a standardized fashion,[18] the absolute value was recorded to the nearest 0.1 cm, and the percentile achieved was estimated by extrapolating this value on the composite head circumference graphs for the appropriate sex published by Nellhaus.[14] These charts show only the means (±2 SDs). Reference values were obtained from the charts as no values were published. Assuming the distribution to be normal, the 10th and 90th percentiles were assigned as 1.3 SDs below or above the mean.

The NCHS percentiles for weight and height are now the recommended reference standard for international comparison and for Australian use.[19,20] More recently, NCHS reference percentiles for head measurement have been published.[15] Head measurements were therefore recoded using NCHS reference values for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles.[15] To determine which standard for OFC might be more useful clinically, for each standard (NCHS and Nellhaus), the proportions of children who changed categories above or below the 10th percentile over time within each group were compared using McNemar tests.[21] Then the proportions below the 10th percentile were compared first between group 3 and groups 1 and 2 combined, and second between groups 1 and 2, by χ^2 analysis.

Percentiles using values from both data sources are ordinal variables, unsuited for multiple regression analysis unless dichotomized; therefore, a continuous variable was computed, as was the ratio of observed to expected OFC, using the NCHS 50th percentile reference[15] for the expected value. The ratios between the three groups at each age were compared using analysis of variance, with linear contrasts to test for differences first between group 3 and groups 1 and 2 combined, and second between groups 1 and 2.

Using the technique developed by Baum and Searls,[22,23] the outline of the head in the OFC plane was determined by molding a malleable metal strip to the contour of the skull; this outline was then traced on paper, the maximum AP and BP diameters were measured, and the cross-sectional area of the head was measured with planimetry. The head measurements were taken in duplicate and mean measurements for each child were entered into a computer.

The configuration of the skull in the occipitofrontal plane was approximately elliptical; the approximate cross-sectional area could therefore be calculated using the measured AP and BP diameters[24] (a description of the method is available on request). This calculated cross-sectional area was compared with the area measured with planimetry. The AP diameter was divided by the BP diameter to give the AP-BP ratio. The mean AP-BP ratio in 8-year-old normal-birth-weight children was 1.279. Assuming an elliptical cross-section to the head, the correction in OFC in groups 1 and 2 was calculated. The cross-sectional area was assumed to remain constant, but the AP-BP ratios were adjusted to the mean (1.279) for the normal-birth-weight children. Measurements of head shape and these calculations were introduced part way through the study; measurements were made on most 8-year-old children in groups 1, 2, and 3 born after October 1, 1980. These data were not available at ages 2 and 5 years and for a few children living out of the state or country who were assessed by other physicians.

The various head measurements at age 8 years were compared between the three groups using analysis of variance, after allowing for differences between boys and girls. Since the head measurements were all highly correlated, the relationship between head measurements at age 8 years and the WISC-R Full Scale IQ was determined using multiple regression analysis. The relationship between the OFC ratio at age 8 years and the WISC-R Full Scale IQ was determined with multiple regression for all children with data at age 8 years, after allowing for differences between the weight groups and sociodemographic variables. The regression coefficients and standard errors for significant variables from the multiple regression analysis were used to calculate 95% confidence intervals (CIs).

Statistical analyses were performed with a computer using Statistical Package for the Social Sciences-X (SPSS-X) programs.[25] Values of $P<.05$ on any statistical test were regarded as statistically significant.

RESULTS

Comparison of NCHS and Nellhaus Reference Values for Head Circumference Below the 10th Percentile

Only children with data at each of the three assessments were included (Table 1); the number of children below the 10th percentile for OFC was compared using first the NCHS and second the Nellhaus reference data. Children in group 1 significantly improved their position relative to the 10th percentile using the NCHS reference between ages 2 and 5 years, but significantly deteriorated using the Nellhaus data. The status of children in group 2 between ages 2 and 5 years remained unchanged using NCHS data, but deteriorated significantly if Nellhaus references were used (Table 1). There were no significant changes between ages 5 and 8 years within any group with either data reference.

Using the NCHS information, proportionally more group 1 children than group 2 children were below the 10th percentile at ages 2 and 8 years. Using the Nellhaus standards at age 2 years, the head growth appeared to be satisfactory with only 6% and 4% of group 1 and group 2 children, respectively, below the 10th percentile, a nonsignificant difference. Although the proportions of children below the 10th percentile at ages 5 and 8 years rose in both groups, the difference between groups 1 and 2 remained nonsignificant using the Nellhaus standards. Comparing group 3 with groups 1 and 2 combined, proportionally fewer group 3 children were below the 10th percentile at both ages 2 and 8 years using the NCHS reference, but only at age 8 years using the Nellhaus data.

Analysis of Variance Results for OFC Ratios at Ages 2, 5, and 8 Years

The OFC ratios, computed using the 50th percentile for the appropriate gender from the NCHS charts, followed a consistent pattern across the three groups at each age (Table 2). Group 3 had significantly higher OFC ratios than groups 1 and 2 combined, and group 1 had significantly lower OFC ratios than group 2. For average 8-year-olds, the differences in OFC between the groups were approximately 1 cm larger in group 3 than in groups 1 and 2 combined, and approximately 1 cm smaller in group 1 than in group 2.

Head Measurements at Age 8 Years

Head measurements other than OFC for those children with data in all the groups are shown in Table 3. The AP diameter, BP diameter, and measured cross-sectional area

Table 1.—Comparisons Using National Center for Health Statistics (NCHS) and Nellhaus[14] Reference Values Between Children With Occipitofrontal Head Circumference Below the 10th Percentile*

	No. (%) of Children <10th Percentile			Comparisons			
				Groups 1 and 2		Group 3 and 1 and 2 Combined	
Reference Value	Group 1 (n=72)	Group 2 (n=90)	Group 3 (n=37)	χ^2	*P*	χ^2	*P*
NCHS							
Age, y							
2	31 (43)	16 (18)	3 (8)	11.2	<.001	5.9	<.02
5	19 (26)†	17 (19)	3 (8)	...	...	...	...
8	22 (31)	13 (14)	1 (3)	5.2	<.05	6.0	<.02
Nellhaus							
Age, y							
2	4 (6)	4 (4)	0 (0)	...	...	...	...
5	13 (18)‡	11 (12)§	2 (5)	...	...	...	...
8	17 (24)	13 (14)	1 (3)	...	...	4.6	<.05

*Only children with data at all ages were included. Group 1 includes children with birth weight between 500 and 999 g; group 2, children with birth weight between 1000 and 1499 g; and group 3, children with birth weight greater than 2500 g. No changes between ages 5 and 8 years were significant within any group.

†Percentile improvement in group 1 children between ages 2 and 5 years based on NCHS value, *P*=.0005.

‡Percentile deterioration in group 1 children between ages 2 and 5 years based on Nellhaus value, *P*=.012.

§Percentile deterioration in group 2 children between ages 2 and 5 years based on Nellhaus value, *P*=.016.

Table 2.—Comparison of Occipitofrontal Circumference (OFC) Ratios at Ages 2, 5, and 8 Years*

Age at Presentation	Group 3	Groups 1 and 2 Combined	Group 1	Group 2
2 years				
No.	48	180	76	104
Mean (SD) OFC/Ratio	0.998 (0.029)	0.986 (0.030)	0.975 (0.027)	0.994 (0.030)
R^2	2.9%		7.2%	
P	.003		<.0001	
5 years				
No.	42	175	75	100
Mean (SD) OFC/Ratio	1.010 (0.030)	0.990 (0.032)	0.981 (0.028)	0.997 (0.034)
R^2	5.5%		4.5%	
P	.0002		.001	
8 years				
No.	50	174	77	97
Mean (SD) OFC/Ratio	1.008 (0.031)	0.990 (0.032)	0.979 (0.028)	0.999 (0.033)
R^2	5.2%		7.0%	
P	.0002		.0001	

*R^2 is the percentage of variance explained by difference between groups.

were all significantly higher in boys; AP-BP ratio was not related to gender. Allowing for differences between boys and girls, the heads of VLBW children were progressively narrower but not longer (in the AP diameter) than those of normal-birth-weight children, and heads of group 1 children were narrower but not longer than those of group 2 children. Consequently, the AP-BP ratios progressively increased and the measured area decreased significantly with decreasing birth weight.

Comparison of Measured and Computed Cross-sectional Areas

Within each of the individual three groups, the computed and observed mean cross-sectional areas in the occipitofrontal plane were almost identical, the largest difference being only −1.2% in group 2; even for individuals in the study, no difference exceeded ±5.3%.

Correction of OFC for Dolichocephaly

The reduction in OFC produced by adjusting for dolichocephalic head shape was greater than 1 cm in only three children; all had AP-BP ratios in excess of 1.4. The reductions of the calculated OFC for increasing AP-BP ratios were as follows: −0.3 cm for a ratio of 1.35; −0.6 cm for a ratio of 1.40; −0.9 cm for a ratio of 1.45; and −1.2 cm for a ratio of 1.50. We concluded that correction of head circumference at age 8 years was not of practical importance for the group, and for the individual was important only for the extremely dolichocephalic head.

WISC-R Full Scale IQ and Head Measurements

The various head measurements were highly correlated (Table 4); some were significantly associated with the WISC-R Full Scale IQ. However, on stepwise multiple re-

Table 3.—Head Measurements at Age 8 Years*

	Mean (SD) Measurements			Statistical Significance			
				Groups 3 vs 1 and 2		Groups 1 vs 2	
Variable	Group 1 (n=17)	Group 2 (n=86)	Group 3 (n=48)	R^2	P	R^2	P
Anteroposterior diameter, cm	18.35 (0.88)	18.46 (0.68)	18.38 (0.72)	NS	NS	NS	NS
Biparietal diameter, cm	13.44 (0.45)	13.92 (0.64)	14.39 (0.64)	12.0%	.0001	3.6%	.007
AP-BP ratio	1.365 (0.051)	1.328 (0.064)	1.279 (0.061)	14.5%	.0001	2.8%	.026
Measured area, cm²	196.3 (12.8)	204.3 (13.9)	208.7 (14.0)	2.4%	.005	2.1%	.046

*R^2 is the percentage of variance explained by difference between groups, and AP-BP ratio, the ratio of anteroposterior to biparietal diameters. NS indicates not significant.

Table 4.—Correlations Between Wechsler Intelligence Scale for Children–Revised Full Scale IQ and Head Measurements in 103 Very-Low-Birth-Weight and 48 Normal-Birth-Weight Children

Head Measurement	r	P
Occipitofrontal circumference ratio	.24	.003
Measured cross-sectional area	.23	.004
Anteroposterior diameter	.19	.019
Biparietal diameter	.20	.013
Anteroposterior/biparietal ratio	−.05	.5 (NS)*

*NS indicates not significant.

gression analysis, the OFC ratio was statistically best related to the WISC-R Full Scale IQ ($R^2=.057$; regression coefficient, 104.2 IQ units; 95% CI, 36.0 to 172.4; $P=.003$). Once the OFC ratio entered the analysis, the remaining head measurements became nonsignificant.

WISC-R Full Scale IQ and OFC Ratio After Adjusting for Birth-Weight Group and Sociodemographic Variables

Since the OFC ratio was the head measurement most highly correlated with the WISC-R Full Scale IQ, the stepwise multiple regression analysis was repeated for all 8-year-old children for whom an OFC measurement and a WISC-R Full Scale IQ was available, after adjusting for birth-weight group differences and sociodemographic data. The WISC-R Full Scale IQ was significantly higher in children with mothers with more years of schooling (+8.2 IQ units; 95% CI, 4.1 to 12.3; $P=.001$), higher social class (+5.9 IQ units; 95% CI, 1.8 to 10.0; $P=.005$), and in group 3 than in groups 1 and 2 combined (+7.8 IQ units; 95% CI, 3.3 to 12.3; $P=.0008$); the WISC-R Full Scale IQ was significantly lower in group 1 than in group 2 (−6.2 IQ units; 95% CI, −1.9 to −10.5; $P=.005$). Allowing for all of the statistically important variables, the OFC ratio remained positively correlated with the WISC-R Full Scale IQ, but less statistically significant (additional $R^2=.016$; regression coefficient, 64.5 IQ units; 95% CI, 5.3 to 123.7; $P=.034$). The total variance explained by these statistically significant variables was 24.2%. There was no significant interaction between birth-weight group and OFC ratio. Other nonsignificant variables were gender, immigrant status, and fee-paying status.

COMMENT

By age 10 years, the OFC reaches about 90% of adult size.[26] In our study, we are therefore dealing with values close to those expected in adult life. This is quite unlike 8-year-old weight and height measurements in which large increases are expected to occur during puberty.

The choice of reference values in assessing OFC is clearly of crucial importance at age 2 years in our study. Diametrically opposed conclusions can be drawn with normal OFC values using the Nellhaus reference standard or poor head growth using the NCHS standards. At ages 5 and 8 years, however, the choice of reference values was rather less important. Roche et al[15] compared the NCHS and Nellhaus charts; the former were appreciably higher at age 2 years. This explains the poorer head growth of VLBW children in our study based on the NCHS reference values. Our observation of an apparent deterioration of head growth in VLBW children between ages 2 and 5 years was unexpected. The use of an inappropriate reference standard (Nellhaus instead of NCHS) now seems a more likely explanation than the normalization of extremely dolichocephalic heads during this time, as previously postulated.[8] As the World Health Organization has recommended NCHS standards for weight and height for international comparisons, standards derived from the same study appear logical also for OFC. The results from our study suggest that the NCHS standards would be more appropriate, particularly in early childhood. However, we have not relied exclusively on the NCHS standards to assess our VLBW children, but have also compared them with our normal-birth-weight children.

The simple technique used to obtain an outline of the head shape was first described by Baum and Searls.[22,23] Although computed tomography or magnetic resonance imaging would supply more precise information, these procedures are ethically and financially unacceptable in the absence of a clinical indication. The good agreement in our study between the measured cross-sectional area and that computed from the AP and BP diameters confirms that this simple technique is sufficiently accurate for clinical purposes. Elliman et al[27] measured the skull diameters using calipers, but did not measure cross-sectional area.

In the first 18 months of life, when the AP-BP ratio is higher than that in the children in our study who were older, Baum and Searls[23] demonstrated that correction of OFC was of clinical importance; our findings indicate that in 8-year-old children, calculated OFC correction had only possible clinical importance only in a small minority of children in whom the AP-BP ratio exceeded 1.4. The typical deformation of the head in premature infants starts shortly after birth and progresses.[23] As Cartlidge and Rutter[28] demonstrated, the dolichocephalic shape of the head is preventable. Having a low priority among the competing demands of treating a critically ill infant, this intervention was used only sporadically in our nursery.

At age 8 years, the WISC-R Full Scale IQ was significantly related to the OFC ratio in both VLBW and normal-birth-weight children. Ross et al[5] also noted a correlation of OFC and the WISC-R in 7-year-old VLBW children. Regression analyses, however, indicated that in our study cohort, social factors emerged as more important associations than head dimensions, although OFC was still a significant association. The AP-BP ratio was unrelated to the WISC-R Full Scale IQ, confirming the conclusion of Elliman et al[27] that in this respect at least, the narrowness of the heads of preterm infants does not matter.

Hack et al[12] recently reported an association in VLBW children between subnormal head circumference at age 8 months and poor cognitive function, including IQ, at age 8 to 9 years. As in our study, poor head growth and IQ were related even after allowing for sociodemographic and other confounding variables. One problem common to the study of Hack et al[12] and our own is the lack of uniform data on cranial sonography since both studies had some children who were born before cranial sonography was introduced into the respective nurseries. Although we cannot ascribe a cause-and-effect relationship between the OFC ratio and IQ, Hack et al[12] postulate that poor growth of the brain up to 8 months of postnatal age may be crucial to subsequent cognitive function.

It was not a primary aim of our study to determine the magnitude of the effect of social class or maternal schooling on IQ; they were included in the regression analyses because they were strongly related to IQ and they may have influenced the relationship between OFC and IQ. Although we dichotomized social class and maternal schooling in the regression analysis for simplicity, no statistical conclusions were altered by allowing for more categories of social class or maternal schooling.

In conclusion, the NCHS data for OFC were more appropriate than the Nellhaus data in our cohorts of VLBW and ELBW children. Head growth achieved by age 8 years was progressively reduced in lower-birth-weight categories in all measurements except AP diameter. Sociodemographic variables and birth-weight group differences were statistically more related to IQ than any head dimension; of the head measurements, OFC was the one most related to IQ. Head measurements other than OFC and correction of OFC for dolichocephaly cannot be recommended in routine clinical practice.

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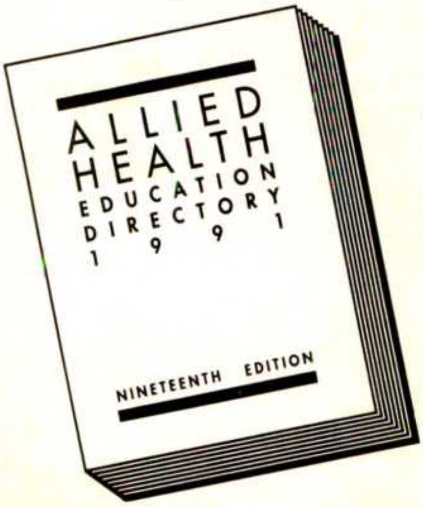

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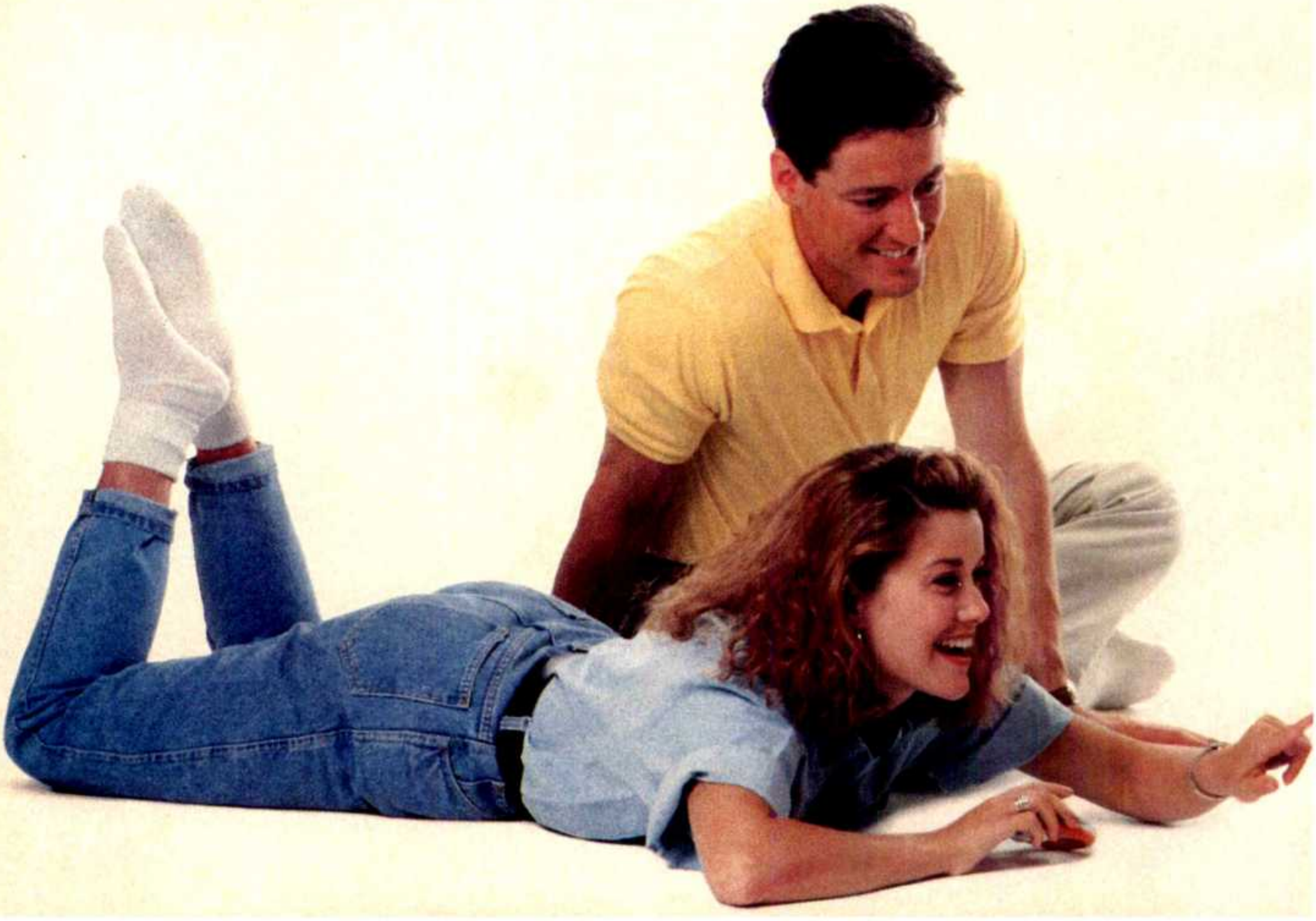

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IPOL™ (POLIOVIRUS VACCINE INACTIVATED)

DESCRIPTION: IPOL™, Poliovirus Vaccine Inactivated, produced by Pasteur Mérieux Sérums & Vaccins S.A., is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). The viruses are grown in cultures of VERO cells, a continuous line of monkey kidney cells, by the microcarrier technique. The viruses are concentrated, purified, and made noninfectious by inactivation with formaldehyde. Each sterile immunizing dose (0.5 ml) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus, determined by comparison to a reference preparation. The poliovirus vaccine is dissolved in phosphate buffered saline. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin and polymyxin B are used in vaccine production, and although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin and 25 ng polymyxin B per dose may still be present. The vaccine is clear and colorless and should be administered subcutaneously.

CLINICAL PHARMACOLOGY: IPOL is a highly purified, inactivated poliovirus vaccine produced by microcarrier culture.[1,2] This culture technique and improvements in purification, concentration and standardization of poliovirus antigen have resulted in a more potent and more consistently immunogenic vaccine than the Poliovirus Vaccine Inactivated which was available in the U.S. prior to 1988. These new methods allow for the production of vaccine that induces antibody responses in most children after administering fewer doses[3] than with vaccine available prior to 1988.

Studies in developed[3] and developing[4,5] countries with a similar inactivated poliovirus vaccine produced by the same technology have shown that a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer.

A study in the U.S. was carried out, which involved 219 two-month-old infants who had received three doses of Poliovirus Vaccine Inactivated manufactured by the same process as IPOL except the cell substrate was primary monkey kidney cells. Seroconversion to all three Types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine. Following a third dose of vaccine at 18 months of age, high titers of neutralizing antibody were present in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses.[6]

Additional studies were carried out in the U.S. with IPOL. Results were reported for 120 infants who received two doses of IPOL at 2 and 4 months of age. Of these 120 children, detectable serum neutralizing antibody was induced after two doses of vaccine in 98.3% (Type 1), 100% (Type 2) and 97.5% (Type 3) of the children. In 83 children receiving three doses at 2, 4, and 12 months of age detectable serum neutralizing antibodies were detected in 97.6% (Type 1) and 100% (Types 2 and 3) of the children.[7,8]

Poliovirus Vaccine Inactivated reduces pharyngeal excretion of poliovirus.[9-12] Field studies in Europe have demonstrated immunity in populations thoroughly immunized with another IPV.[13-17] A survey of Swedish children and young adults given a Swedish IPV demonstrated persistence of circulating antibodies for at least 10 years to all three types of poliovirus.[13]

Paralytic polio has not been reported in association with administration of Poliovirus Vaccine Inactivated.

INDICATIONS AND USAGE: Poliovirus Vaccine Inactivated is indicated for active immunization of infants, children and adults for the prevention of poliomyelitis. Recommendations on the use of live and inactivated poliovirus vaccines are described in the ACIP Recommendations[18,19] and the 1988 American Academy of Pediatrics Red Book.[20]

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations: It is recommended that all infants, unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.[18] Poliovirus Vaccine Inactivated should be offered to individuals who have refused Poliovirus Vaccine Live Oral Trivalent (OPV) or in whom OPV is contraindicated. Parents should be adequately informed of the risks and benefits of both inactivated and oral polio vaccines so that they can make an informed choice (Report of An Evaluation of Poliomyelitis Vaccine Policy Options, Institute of Medicine, National Academy of Sciences, Washington, D.C., 1988).

OPV should not be used in households with immunodeficient individuals because OPV is excreted in the stool by healthy vaccinees and can infect an immunocompromised household member, which may result in paralytic disease. In a household with an immunocompromised member, only Poliovirus Vaccine Inactivated should be used for all those requiring poliovirus immunization.[20]

Children Incompletely Immunized: Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see DOSAGE AND ADMINISTRATION).

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with Poliovirus Vaccine Inactivated.

ADULTS

General Recommendations: Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the U.S. is not recommended. Adults who have increased risk of exposure to either vaccine or wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the DOSAGE AND ADMINISTRATION section.[18]

The following categories of adults run an increased risk of exposure to wild polioviruses:[19]

- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health care workers in close contact with patients who may be excreting polioviruses.
- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.
- Incompletely vaccinated or unvaccinated adults in a household (or other close contacts) with children given OPV provided that the immunization of the child can be assured and not unduly delayed. The adult should be informed of the small OPV related risk to the contact.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

Patients with recognized immunodeficiency are at greater risk of developing paralysis when exposed to live poliovirus than persons with a normal immune system. Under no circumstances should oral live poliovirus vaccine be used in such patients or introduced into a household where such a patient resides.[18]

Poliovirus Vaccine Inactivated should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of Poliovirus Vaccine Inactivated.[21]

CONTRAINDICATIONS: Poliovirus Vaccine Inactivated is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including neomycin, streptomycin and polymyxin B.

If anaphylaxis or anaphylactic shock occurs within 24 hours of administration of a dose of vaccine, no further doses should be given.

Vaccination of persons with any acute, febrile illness should be deferred until after recovery; however, minor illnesses such as mild upper respiratory infections are not in themselves reasons for postponing vaccine administration.

WARNINGS: Neomycin, streptomycin, and polymyxin B are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see DESCRIPTION) and allergic reactions may occur in persons sensitive to these substances.

PRECAUTIONS: General: Before injection of the vaccine, the physician should carefully review the recommendations for product use and the patient's medical history including possible hypersensitivities and side effects that may have occurred following previous doses of the vaccine.

Epinephrine hydrochloride (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Concerns have been raised that stimulation of the immune system of a patient with HIV infection by immunization with inactivated vaccines might cause deterioration in immunologic function. However, such effects have not been noted thus far among children with AIDS or among immunosuppressed individuals after immunizations with inactivated vaccines. The potential benefits of immunization of these children outweigh the undocumented risk of such adverse events.[18]

Drug Interactions: There are no known interactions of Poliovirus Vaccine Inactivated with drugs or foods. Simultaneous administration of other parenteral vaccines is not contraindicated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY: REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C. Animal reproduction studies have not been conducted with Poliovirus Vaccine Inactivated. It is also not known whether Poliovirus Vaccine Inactivated can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Poliovirus Vaccine Inactivated should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE: Safety and efficacy of IPOL have been shown in children 6 weeks of age and older[6,8] (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed during a clinical trial.[6] Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures ≥39°C (≥102°F) were reported in up to 38% of vaccinees. Other symptoms noted included sleepiness, fussiness, crying, decreased appetite, and spitting up of feedings. Because Poliovirus Vaccine Inactivated was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given without IPV.

In another study using IPOL in the United States, there were no significant local or systemic reactions following injection of the vaccine. There were 7% (6/86), 12% (8/65) and 4% (2/45) of children with temperatures over 100.6°F, following the first, second and third doses respectively. Most of the children received DTP at the same time as IPV and therefore it was not possible to attribute reactions to a particular vaccine; however, such reactions were not significantly different than when DTP is given alone.

Although no causal relationship between Poliovirus Vaccine Inactivated and Guillain-Barré Syndrome (GBS) has been established,[22] GBS has been temporally related to administration of another Poliovirus Vaccine Inactivated.

NOTE: The National Childhood Vaccine Injury Act of 1986 requires the keeping of certain records and the reporting of certain events occurring after the administration of vaccine, including the occurrence of any contraindicating reaction. Poliovirus Vaccines are listed vaccines covered by this Act and health care providers should ensure that they comply with the terms thereof.[23]

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration. If these conditions exist, vaccine should not be administered.

After preparation of the injection site, immediately administer the vaccine subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In adults the vaccine should be administered in the deltoid area.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

CHILDREN

Primary Immunization: A primary series of IPOL consists of three 0.5 ml doses administered subcutaneously. The interval between the first two doses should be at least four weeks, but preferably eight weeks. The first two doses are usually administered with DTP immunization and are given at two and four months of age. The third dose should follow at least six months but preferably 12 months after the second dose. It may be desirable to administer this dose with MMR and other vaccines, but at a different site, in children 15-18 months of age. All children who received a primary series of Poliovirus Vaccine Inactivated, or a combination of IPV and OPV, should be given a booster dose of OPV or IPV before entering school, unless the final (third dose) of the primary series was administered on or after the fourth birthday.[18]

The need to routinely administer additional doses is unknown at this time.[18]

A final total of four doses is necessary to complete a series of primary and booster doses. Children and adolescents with a previously incomplete series of IPV should receive sufficient additional doses to reach this number.

ADULTS

Unvaccinated Adults: For unvaccinated adults at increased risk of exposure to poliovirus, a primary series of Poliovirus Vaccine Inactivated is recommended. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, 3 doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. If less than 1 month is available, a single dose of either OPV or IPV is recommended.

Incompletely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than 3 doses of conventional IPV or a combination of conventional IPV or OPV totalling fewer than 3 doses should receive at least 1 dose of OPV or Poliovirus Vaccine Inactivated. Additional doses needed to complete a primary series should be given if time permits.

Completely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of either OPV or IPV.[19]

HOW SUPPLIED: Syringe, 0.5 ml with integrated needle (1 x 1 Dose package and 10 x 1 Dose package) — Product Nos. 49281-8605-1 and 49281-8605-2.

STORAGE: The vaccine is stable if stored in the refrigerator between 2°C and 8°C (35°F and 46°F). *The vaccine must not be frozen.*

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Educational Intervention

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Teaching Rounds in an Inpatient Pediatric Service

Rhona Shulman, MA; LuAnn Wilkerson, EdD; Donald A. Goldman, MD

• Teaching rounds are a mainstay of most educational programs for interns and residents, but little is known about how they are conducted and the role they play in house staff members' learning. We performed a qualitative study of teaching rounds in an inpatient adolescent service using five data sources: observations, interviews, house staff ratings, results of a house staff retreat, and documents outlining faculty responsibilities. Interns, senior residents, and faculty members expressed differing views regarding the purpose, process, and content of rounds; mutual roles and expectations; and time management. An interactive teaching format focused around the visit of a patient to the conference room stimulated house staff interest and learning to a greater extent than did more traditional case presentations and lectures. These results suggest a need to develop a consensus among faculty and house staff regarding the purpose, content, and process of rounds.

(*AJDC.* 1992;146:55-60)

Recent changes in health policy and medical technology have had dramatic effects on pediatric practice, particularly on the inpatient services of teaching hospitals. However, educational practices on pediatric inpatient wards have changed little in response to these rapid changes in health care. In particular, attending physicians' teaching rounds have remained a sacrosanct fixture in most pediatric training programs. These rounds have not been evaluated rigorously as an educational approach, and little is known about their role in house staff or student learning. In a recent study, Hilliard[1] identified "good and effective" teaching behaviors in postgraduate pediatrics, but did not link them to specific educational activities or objectives. In contrast, internal medicine teaching rounds have been subjected to systematic study at a number of institutions.[2-7]

This study examines the goals of teaching rounds in a large pediatric teaching hospital as viewed by both attending physicians and house officers, to document what actually occurs on rounds, and to determine whether specific activities meet perceived learning needs. It was hoped that faculty and residents would be able to use the study as a springboard for redefining the process and purpose of rounds.

MATERIALS AND METHODS

Children's Hospital, Boston, Mass, is a university-affiliated pediatric teaching hospital with a 68-bed inpatient general medical service divided among three age-based wards: infant/toddler, school age, and adolescent/young adult. In response to the rapidly changing nature of inpatient pediatric care, supervision of these wards was restructured in 1986 based on a model adapted from the British system of "firms."[8] Both practitioner and specialist faculty members serve as attending physicians once annually, during which time they are responsible for daily meetings with students, teaching rounds with house staff members and students three to four times per week, and direct care of all patients who do not have a private physician.

This study was conducted at the Charles Alderson Janeway Service for adolescents and young adults, on which one of the authors (D.A.G.) is the service chief. In 1988, formal house staff evaluations of the educational program in the firm suggested that teaching rounds were not meeting the learning needs of residents. House officers were particularly critical of the lack of clear educational goals, feedback, and bedside teaching.

This study of pediatric teaching rounds was conducted in the winter of 1989 to 1990. During the study, four pediatric attending physicians, seven interns, and three senior residents were assigned to the Janeway service. Although a number of medical students rotated through the service, they were not included in

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC.*

Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

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the analysis because the focus was on house staff education. Teaching rounds were held three times per week for 1½ hours.

A qualitative research approach was selected as the most appropriate strategy for elucidating the everyday activities related to teaching rounds and for developing knowledge for the improvement of educational practice.[9-11] Although qualitative research is still relatively new in medicine, it has been effectively used in previous studies of clinical teaching.[12-14]

Qualitative techniques emphasize the meanings that the activities being studied have for the participants. Data collection methods provide information on the physical, social, and intellectual context within which the activities occur, permitting evaluation of the complex interrelatedness of events rather than deliberately isolating and manipulating single variables. Such research is inductive, with empirical observations preceding the formation of hypotheses, which are usually expressed in the language of the subjects. Finally, qualitative research is consciously subjective, focusing on the viewpoints of the various participants and controlling for individual bias using a variety of verification and validation procedures throughout the course of the study.

Data for the study were collected in five ways: review of written documents concerning educational programs at the service ("Responsibilities of the Attending Physician on the Janeway Service"[15] and "A Brief Guide to the Janeway Curriculum"[16]), direct observation of eight teaching round sessions, review of 2 years of formal ratings of faculty members' teaching by the house staff, interviews with attending physicians and house staff members, and a report from the chief resident concerning the results of a house staff retreat held in September 1989.

Formal ratings of the faculty's teaching, which were completed by 62% of house officers rotating in the Janeway service from January 1988 to January 1990, included 12 descriptions of effective teaching behavior for which respondents indicated the degree to which the attending physician's teaching was characterized by these behaviors. Ratings were based on a seven-point Likert scale on which seven indicated "strongly agree." Six additional questions regarding curricular issues required a frequency response. House officers were also asked to indicate whether they had received instruction in each of the 38 topics composing the curriculum of the Janeway service. The rating form was developed by one of the authors (D.A.G.) and reflected both the characteristics of effective clinical teaching outlined by Irby and Rakestraw[17] and the demands of patient care (eg, caring for assigned patients and serving as a resource for patient care). Although used as a feedback tool for several years, no reliability studies of the rating form have been conducted.

Predominant educational themes identified from the written documents, field notes, and residents' ratings formed the basis of semistructured interviews with three of the four attending physicians, all three senior residents, and five of the seven interns who had participated in the observed sessions. Some individuals were unable to respond because of scheduling conflicts.

RESULTS

The pediatric teaching rounds observed in this study were characterized by four educational features: (1) educational purpose, (2) teaching format, (3) clarity of roles and expectations, and (4) use of available time. These features were often perceived differently by attending physicians and house staff members.

Purpose of Rounds

Written guidelines outlining the purpose of teaching rounds are given to senior residents and attending physicians at the beginning of each rotation on service and include the following description[16]:

> This conference is the cornerstone of the curriculum and provides the principle opportunity for the attending physician to share his or her expertise with the housestaff. Rounds generally should be devoted to a full discussion of one or two particularly interesting or challenging patients . . . "

Nonetheless, interviews with attending physicians revealed a lack of clarity about this purpose. Attending physicians discussed the struggle they felt between teaching medical science or clinical management and between addressing outpatient or inpatient issues. Comments from three attending physicians included the following:

> I don't think that the rounds should be a place for state-of-the-art literature on a regular basis. I was torn by this the other day when I was doing the hyperthyroid patient. I could have brought them references on the most subtle aspects of the treatment of thyrotoxicosis or its molecular biology. The kinds of questions they were asking made it clear that they weren't how to interpret the basic thyroid function tests.

> Three of four interns will not care about amenorrhea. They would be much more interested in looking at the cellular level of the hypothalamus.

> It's hard. They're still learning everything—how to deal with parents, people who are hysterical about their children, about drug choices, tests to request.

Attending physicians also were concerned about whether rounds should or do provide an appropriate opportunity to address nonmedical issues, such as helping house officers to cope with a highly stressful residency experience. These concerns were neither addressed in the Janeway guides nor shared with house staff members.

Interns and residents, on the other hand, expressed views of the attending physician's role as a clinical expert that were consistent with the intended goal outlined in "A Brief Guide to the Janeway Curriculum."[16] Rounds, they suggested, should focus primarily on practical diagnostic, therapeutic, and management issues relevant to specific patients. One intern said, "It's nice to leave attending rounds with a list, a concrete approach to the patients you have, to make your work easier."

Observations and interviews revealed that the purpose of teaching rounds was rarely discussed by participants. Ratings of faculty by house staff members indicated that attending physicians did not clearly spell out their expectations of interns and residents on rounds (mean rating, 4.4 on a scale of 1 to 7).

Format of Rounds

Three different teaching formats were observed during the eight rounds, all of which were conducted entirely in the ward conference room: informal lectures on topics selected from the curriculum (four rounds), case presentations of patients on the service (two rounds), and interviews with patients (two rounds). The principle features of these three teaching formats are summarized in the Table.

Lecture Presentations

These preplanned presentations were based on topics from the curriculum that were relevant to patients currently on the service. The attending physician stood and talked from an outline on the board, hence their description as "chalk talks." The primary purpose of these rounds appeared to be the transmission and recall of topical information. As seen by one attending physician, they were an opportunity to share "a few pearls of wisdom." Occasionally, the attending physicians interjected questions to elicit specific knowledge, eg, "What are the complications you should look for? How do we do it here?" Many of the attending physicians' questions were rhetorical, if not by design, then at least because not enough

Characteristics of Three Approaches to Teaching Rounds Identified During Observations

Format	Leadership	Level of Intern Participation	Focus of Attending Physicians' Questions	Content Focus
Lecture	Directed by attending physician	Low	Knowledge	Curricular topic
Case presentation	Directed by attending physician	Moderate	Patient data, knowledge, problem solving	Diagnosis, management
Patient interview	Initiated by attending physician	High	Problem solving	Diagnosis, interview skills

time was allowed for response. The interns provided most of the answers, which were generally brief, and students participated infrequently. The senior residents asked a few questions of the interns and students and occasionally added personal experiences to illustrate a point made by the attending physician. Although there were no purely didactic presentations, attending physicians varied in the amount of participation they encouraged. On three separate occasions during these rounds, interns were observed to be sleeping.

Feedback from house staff members about these rounds ranged from expressions of appreciation to descriptions of the problems inherent in such an attending physician–directed approach. Following are some of the comments of residents and interns:

> They were mostly expository about some topic, and then questions at the end. My view is that they didn't engage the students and interns and myself enough during the lecture period, and afterwards the students or interns did not ask the most focused questions because it was after the fact.
>
> Interactive lectures work well because you can interject whatever you're thinking or your questions at the time instead of waiting . . . It can be addressed right then.
>
> After so many years of lectures, they're all the same after a while. The only way to remember things is to spice them up.
>
> When you crack open the lecture there is more chance of there being interaction and that's when the students learn the most—and myself.

Case Presentations

These two rounds consisted of a combination of the techniques observed in the "chalk talks" and the patient interviews described in the next section. Both rounds began with an intern's presentation of a complete case. After the presentation, the attending physician led the house staff and students through a discussion of a differential diagnosis while asking questions that required both factual knowledge and clinical problem-solving skills. When the diagnosis had been previously established, the attending physician directed questions to the presenting intern, whose answers often had a rote quality. Few other members of the group participated. When the diagnosis had not been previously established, all members participated in the discussion. When interviewed, house staff members indicated that rounds of this type were standard and usually well received. The questionnaire item most favorably rated by both interns and residents was "Attending used a patient-oriented approach to teaching."

Patient Interviews

Although none of the observed rounds was conducted at bedside, one of the attending physicians brought patients into teaching rounds on two occasions. In one instance, an intern interviewed the patient, and, in the other, the attending physician interviewed the patient, and an intern interviewed the patient's mother. The attending physician stressed the importance of developing interviewing skills appropriate for adolescents.

During the ensuing discussion, all members of the group were involved in trying to understand the clinical significance of what they had heard and seen. The atmosphere on both occasions was dynamic, with multiple interactions between the attending physician and group members, as well as between the house staff members and students.

The attending physician used questions to encourage the members of the group to interpret the historical data collected in the interview, to determine what else they would like to know, and to commit themselves to a diagnosis and plan. When members of the group asked about specific laboratory and physical examination data, he or she used "what if" questions to probe their reasoning processes. For example, rather than telling them that a particular test value was high, the attending physician would ask, "What would you do if I told you that the result was high?"

These patient interviews were extremely well received by the house staff. It was evident that they had rarely, if ever, been exposed to this form of teaching rounds. Residents' comments included the following:

> People left those rounds stimulated.
>
> [With] the tension of trying to state questions or trying to ask questions, people do remember better.
>
> The more interactive the rounds are, the more we learn. There may be less information talked about, but there is more learning in the long run.
>
> It's nice when you can do a little bedside teaching or actually get the patient involved in rounds, because whenever they're involved it's more interesting . . . . I think it keeps everybody more awake, and you have more to discuss afterward when you've all seen the patient . . . so nobody's left out. The discussion is fuller.

Roles and Expectations

Observations suggested that interns were the focus of educational efforts during rounds and were frequently expected to present patient cases and be prepared to answer questions. Because students had separate meetings with attending physicians on faculty, they had no explicit role in teaching rounds. Senior residents contributed to the teaching by asking questions of both the attending physicians and the interns and by providing clinical examples from their own experiences. However, house staff evaluations of attending physicians' teaching suggested that there was little discussion among team members of their roles and expectations at the beginning of the month together. The Janeway guides[15,16] contain no statements regarding the role of the various members of the teaching rounds team. Interviews suggested conflicting expectations between house staff members and attending physicians as well as among house staff members themselves.

Both interns and residents expected attending physicians to be experts in some special area of pediatrics, to share this expertise with the team during rounds, and to periodically come prepared with specific lectures. Senior residents suggested that, unless attending physicians were sufficiently familiar with general issues of adolescent medicine raised in case discussion, they could not be responsive to and interactive with the learners. One intern said, "They have to have the ability to talk off the top of their heads fairly knowledgeably about a fair range of topics." A resident added the following comment:

> If there's a case that comes on and the attending happens to specialize in that area, it makes for a perfect attending rounds; when that doesn't happen, it becomes more difficult, and the team tends to think about what the attending knows something about, trying to figure out what would be a good thing to hear. So, the broader the knowledge base that the attending has, the better.

One intern characterized the choice of topics for rounds as being a conflict between "their (the attending physicians') time" and "our (the house staff's) time." When attending physicians saw themselves as responsible for providing the focus of discussion, rounds became "their time." Such attending physicians might choose to present topics of personal interest or to turn discussions toward their own area of expertise. Alternatively, this intern preferred to view teaching rounds as an opportunity for the interns to present and discuss concerns and issues of relevance to them ("our time"). "The attending is catering to us," the intern said. Other interns agreed that many teaching rounds represented "their time," but were more willing to relinquish control to the attending physician or senior residents, whom they perceived as being more knowledgeable.

All of the senior residents interviewed believed that they shared responsibility for organizing teaching rounds. This role was sometimes fulfilled by selecting topics for presentation at the beginning of their month in the service and inviting guest speakers to lecture about subjects regarding which the attending physician was not perceived to be an expert. On other occasions, senior residents ascertained the teaching needs of the interns on a daily basis and negotiated with the attending physician on a suitable topic or patient for discussion at rounds. One senior resident's comments echoed the theme of "our time" and "their time" when he described his role as "representing" the interns' requests. Two issues raised by senior residents and attending physicians in the interviews suggested that these two groups experienced specific conflicts in roles and expectations, but that these issues were rarely, if ever, discussed. First, there was disagreement concerning how much responsibility the residents had for the conduct of teaching rounds beyond the selection of topics and speakers. All three senior residents saw themselves as responsible for intervening during rounds if discussions became too didactic or were unrelated to the care of patients on the service, but none had discussed this role with the attending physician. One resident said, "Sometimes I try to guide the direction in which the discussion is going to go, especially if there are certain issues about this patient's care on the floor which we want to address." No faculty member mentioned that senior residents shared responsibility for the conduct of teaching rounds.

Second, attending physicians expressed a desire to participate more regularly in early morning work rounds traditionally run by the senior residents. Given increasing demands for accountability and quality assurance, the attending physicians saw work rounds as providing them with an efficient mechanism for keeping up to date on their assigned patients, monitoring the care of all patients on the ward, observing the house staff and students for purposes of feedback, and evaluating the management and teaching skills of the senior residents. One attending physician commented that attendance on work rounds facilitated selection of patients for discussion at teaching rounds. In contrast, senior residents objected strenuously to the presence of attending physicians on work rounds, contending that even if the attending physicians remained silent observers, they would alter the chemistry of the team and subtly undermine the independence and leadership of the senior resident. However, all of the interns said that they appreciated having attending physicians on work rounds and believed that the value of teaching rounds was enhanced when the attending physicians were familiar with all of the patients on the service.

Time Management

Both house staff members and attending physicians noted that rounds rarely started on time and were frequently interrupted. This disrupted discussions and impeded teaching. Indeed, on average, the observed rounds began 20 minutes late. Once the entire group was assembled, there were from one to five "pages" per session. One intern commented:

> Because we are on a beeper, I get beeped out of rounds . . . This is pretty much the only protected time that I don't have to go through a guilt trip of someone saying, you should be doing your job here. The nurses won't be disturbed when *they* are in a meeting.

An attending physician thought rounds should be held in greater respect, saying, "It's a mistake when the senior [resident] doesn't come on time."

Although attending physicians generally held the senior residents responsible for tardiness, there was a general consensus among everyone interviewed that many other demands made it difficult for house staff members to be present, let alone punctual, for teaching rounds. Senior residents noted that their daily report to the physician-in-chief and associate physician-in-chief, which immediately preceded rounds, always ended late. Interns were under intense pressure to complete a tremendous amount of clinical and administrative work. Two attending physicians attributed this situation to the increased number of admissions in recent years:

> Part of the problem is that you've got people [interns] who are phenomenally busy all the time. It used to be that, for rounds at 11, you were never late. The senior was never late. The senior's job was to find the interns and bring them here.
>
> They will have been rounding, they will have 40 minutes to do their busy work, see their patients, answer nursing questions. Then they have to come here, when they may be worrying about some order.

COMMENT

Most pediatric rounds with attending physicians that were observed in this study consisted of canned talks by the attending physician and case presentations by interns, with little opportunity for participant interaction and no teaching at the bedside. Although the house staff was generally satisfied, there was a sense of resignation about the way rounds were conducted. "I accept that is the way it is," remarked one intern. "This is the way things have always been done here," commented one attending physician. There was a lack of clarity and agreement about the purpose of rounds and exactly what was expected of house officers and attending physicians. One intern characterized the confusion as a failure to decide whether rounds were a time for interns to learn about issues of interest to them ("our time") or for attending physicians to teach about their favorite topics ("their time").

It was evident that the movement in undergraduate medical education toward more interactive, student-directed teaching[18] had not yet permeated residency education, at least in this institution. Time pressures, demands for patient care, a reward structure that favors patient care and research at the expense of teaching, and a lack of awareness of educational alternatives have created significant barriers to change.[19]

In this study, even when time was set aside and labeled as educational, both house officers and attending physicians found it difficult to leave their role as caregivers. Rounds began late and were frequently interrupted, and attending physicians expressed concern about not being a part of morning work rounds. Although the study was limited to a large pediatric teaching hospital, the dilemma of the Janeway service is neither unique nor of recent vintage. Twenty-eight years ago, Ebert[20] observed that, in residency education, "Demands for service can impinge on the educational aspects of a program. Repetition of experience may dull the appetite for learning."

In a recent article about the service/education conflict in internal medicine, Wartman et al[21] suggested that adherence to principles of adult learning would result in dramatic changes in residency education. "Recommendations for modifying residency programs have not led yet to critical examination of what constitutes residency *education* as opposed to *training*." Rounds with attending physicians can be examined in light of these principles[22]:

1. Adults are responsible for self-education. What opportunities are provided during rounds for house officers to develop the skills needed for life long learning—accurate self-assessment, effective inquiry, and critical appraisal? Who decides what, how, and when house officers will learn?

2. Adults have accumulated a large reservoir of experience and expertise that serves as an important source of self-identify and a basis for further learning. How is this expertise brought to bear on rounds with attending physicians? Who teaches whom?

3. Adults focus on the resolution of problems rather than the acquisition of information isolated from a meaningful context. How might a case presentation be used as a problem to stimulate learning? Are there other formats for rounds that could be used to raise relevant problems?

In our study, one attending physician demonstrated how teaching rounds might look if attention were paid to these principles. During rounds, he brought in patients, engaged interns in conducting interviews, and involved all team members in making decisions about additional data to be collected to confirm or discard diagnostic possibilities. The problems presented by the patients were new, unfamiliar, and compelling. During the discussion, everyone participated by both asking and answering questions, teaching one another. House staff members commented about the value and excitement of these sessions.

The attending physicians on the Janeway service questioned the purpose of teaching rounds as currently conducted, but only one of the four had acted. He did so by changing his approach in teaching rounds "from telling them what I think they need to know, to responding to what they think they need to know." He attributed the failure of his colleagues to take action to a lack of knowledge of or skill in using alternative teaching approaches, the comfort of the familiar, or too little encouragement to take teaching seriously. One attending physician said:

> We should meet as a faculty and discuss these issues about rounds and curriculum and style. We should be a minifaculty like we would were we a college faculty. What works? What doesn't work? What could we do better? We don't get together as a group to discuss our teaching. I think we should, several times a year.

In April 1990, the Janeway service conducted a retreat for faculty members to consider the results of this study. Noting that the discussion of logistic issues had occupied most of the morning, a senior attending physician suggested that the faculty was "waltzing around the real issue. Perhaps the whole business of attending rounds has become obsolete." Drawing from his experience as a tutor in new problem-based medical student curriculum at Harvard Medical School,[23] he argued that, because teaching could not be equated with learning, educational sessions should focus less on the oral transmission of knowledge and more on the development of critical thinking and decision-making skills. "Set it up so that you can hear how the interns think," he said. A subcommittee has developed a proposal for changing the curriculum of the residency, including incorporation of new models for teaching rounds.

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Stone J. *In the Country of Hearts: Journeys in the Art of Medicine.* New York, NY: Delacorte Press; 1990:15-19.

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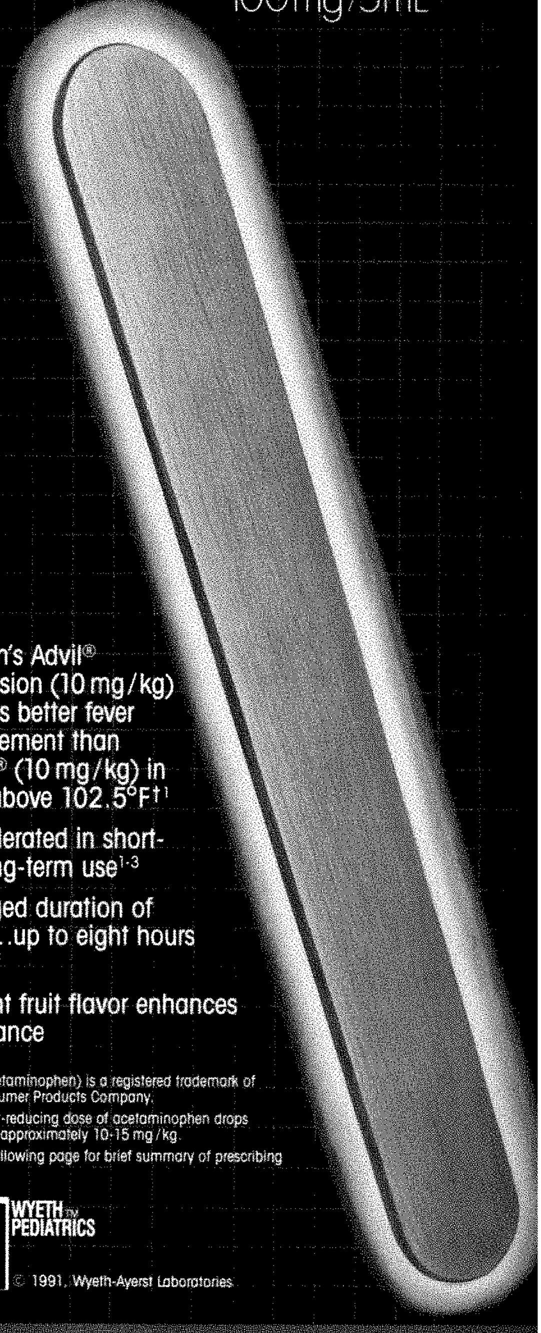

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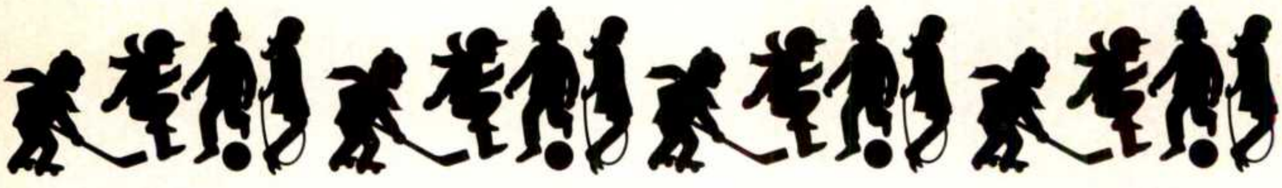

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PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time.

CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions. Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 6 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis, fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coomb's positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (eg., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children), 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

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Body Size and Composition of Perimenarchal Girls

Gilbert B. Forbes, MD

• A number of measurements are reported on a cross-sectional sample of girls who were studied at times ranging from 54 months prior to menarche to 82 months after menarche. Included are anthropometric measurements, lean weight, body fat, abdomen-hip ratio, skeletal size, bone age, muscle strength, and urinary hydroxyproline excretion. The years preceding menarche are associated with an array of physiological and anatomical changes, making it difficult to assign a causative role to any one of them.

(*AJDC.* 1992;146:63-66)

In the course of a study of body composition in normal schoolchildren,[1] we collected a substantial amount of data on various aspects of body composition, bone maturation, puberty status, and anthropometric measurements.

SUBJECTS AND METHODS

Subjects

We report on a subset of 113 girls for whom age at menarche was known. They were white suburban girls who attended school regularly and had no evidence of significant disease. Their ages at the time our measurements were made ranged from 54 months before menarche to 82 months after menarche. Menarchal age ranged from 10.3 to 15.8 years (average±SD, 12.8±1.14 years). The following data illustrate the timing of a number of events that take place during the perimenarchal years.

Methods

Age at menarche was obtained by direct questioning of postmenarchal girls. In the case of premenarchal girls, we telephoned the family every few months until menstruation began. In this way, each girl was classified according to the difference between chronological age when measurements were made and menarchal age.

Height was measured by the Holtain stadiometer and weight on platform scales, with the subject dressed in cotton pajamas and paper slippers. The body-mass index is weight in kilograms divided by height squared in meters. Lean body mass was estimated by potassium 40 counting.[1] Body fat is weight minus lean body mass. For measurement of sitting height, the subject sits on a wooden box of known height with her back next to the stadiometer. Hand span is the distance between the tip of the thumb and the tip of the fifth finger with the hand outstretched against a ruler. Skinfold thickness is the average of measurements in the triceps, biceps, and subscapular regions (Harpenden caliper).

Abdominal circumference was measured at the level of the umbilicus with a steel tape, with the subject standing erect and breathing normally. Hip circumference was measured at the point of maximum protuberance of the buttocks. Handgrip strength was measured on the dominant hand with a hand dynamometer. Three measurements were made at intervals of several minutes, and the highest one was used for analysis (of incidental interest, the reading taken with the subjects clothed was almost always higher than when they were in pajamas).

For sexual maturity, breast and pubic hair stages were rated according to the method of Tanner.[2] Bone age was assessed from a roentgenogram of the left wrist and hand according to the criteria of Gruelich and Pyle[3]; x-ray tube distance, 102 cm. For metacarpal cortex cross-sectional area, the inner and outer cortex diameters at the midpoint of the second left metacarpal bone were measured on the roentgenogram with a Helios caliper, from which the area $= (\pi/4) \times (OD^2 - ID^2)$.[4] For metacarpal cortex volume, the internal and external diameters of the cortex of the second metacarpal bone are measured (Helios caliper) on the roentgenogram at the point of greatest convexity together with the length of the cortex and the diameter at each end of the cortex. The distal and proximal halves of the cortex are each considered as the frusta of two cones, one defined by the periosteal surface, the other (a hollow cone) by the endosteal surface. The measurement sites are shown in Fig 1.

The volume of the outer proximal cone frustum is here

$$(1)\quad \left(\frac{\pi}{3} h_1\right) \times (r_2^2 + r_2 r_3 + r_3^2),$$

where r indicates the radius and h indicates the height, and the volume of the distal outer cone frustum is

$$(2)\quad \left(\frac{\pi}{3} h_2\right) \times (r_2^2 + r_2 r_3 + r_3^2).$$

The sum of these two equations is total volume of the bone cortex plus the marrow. The volumes of the inner cone frusta are calculated in similar fashion, substituting r_1 for r_2 in the equations above. The total cortex volume is the difference between the volumes of the outer and inner cone frusta. This technique assumes that the metacarpal cortex is geometrically equivalent to two regular flat-topped cones (ie, frusta of cones) placed end to end.

For urinary hydroxyproline excretion, a spot urine sample was analyzed for urinary hydroxyproline and creatinine concentrations. An estimate of 24-hour urinary hydroxyproline excretion was derived as follows: Twenty-four–hour urine creatinine excretion was estimated from lean body mass by the formula of Forbes and Bruining.[5] Then 24-hour urinary hydroxyproline excretion is equal to the urinary hydroxyproline–creatinine ratio times the calculated 24-hour creatinine excretion. Hydroxyproline excretion is an index of bone turnover.

The age distribution of subjects is shown in the Table.

RESULTS

The results are shown in the figures, where the various measurements are plotted as a function of the difference between chronological age when the measurements were done and age at menarche. Negative values represent premenarchal and positive values postmenarchal girls. All of the data are cross-sectional in nature.

Figure 2 shows the steady progression in stature,

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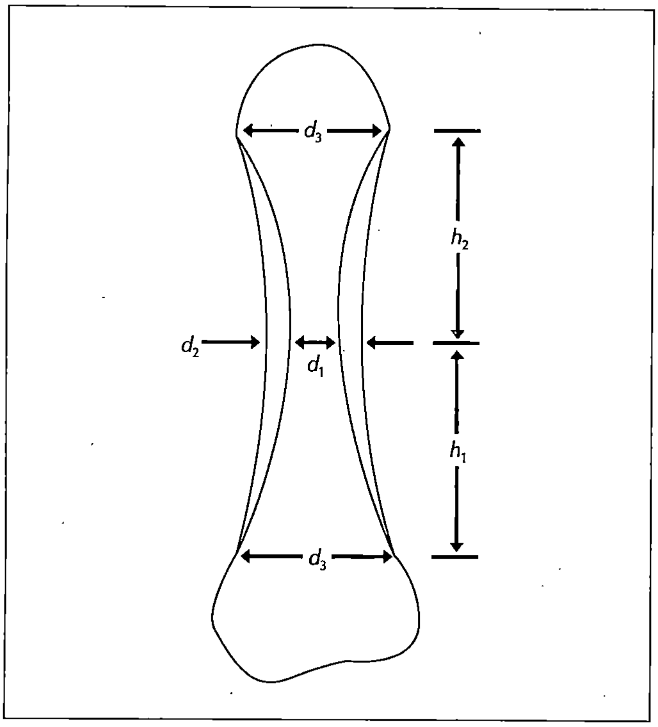

Fig 1.—*Diagram of metacarpal bone, showing location of measurements (d indicates diameter; h, height) necessary for calculating total volume of the cortex from the equations in the "Methods" section. While the shape of the entire cortex resembles a "hyperboloid of one sheet" rather than the frusta of two cones placed end to end, the use of the latter would seem to be a reasonable approximation. From Forbes,[1] with permission.*

Description of Subjects*

Group	No. of Subjects	Difference Between Chronological Age and Maternal Age, mo: Average	Difference Between Chronological Age and Maternal Age, mo: Range	Range of Chronological Ages, y
1	4	–46	–54 to –41	8 4/12 to 10 1/2
2	12	–27	–33 to –23	9 3/12 to 12 7/12
3	13	–14	–19 to –9	10 9/12 to 13 3/12
4	15	–1.5	–6 to +3	10 2/12 to 14 11/12
5	10	+11	+7 to +17	12 2/12 to 17 3/12
6	10	+24	+18 to +29	14 1/12 to 16 10/12
7	17	+36	+31 to +41	13 5/12 to 17 5/12
8	15	+50	+44 to +54	14 3/12 to 17 8/12
9	11	+60	+55 to +64	16 3/12 to 18 5/12
10	6	+74	+70 to +82	17 4/12 to 17 11/12

*n = 113.

weight, lean body mass, body fat, and Tanner stage for breast and pubic hair during the premenarchal years. Indeed, in absolute terms, the average increase in lean weight prior to menarche is greater than the increase in body fat (11 vs 2.5 kg) in this group of girls. As expected, there was a steady progression in breast and pubic hair development.

In this group of girls, maximum stature was achieved by 1 year after menarche, and, if one excludes the oldest group, the same is true for weight and lean body mass. However, body fat continued to increase, at a rather slow rate.

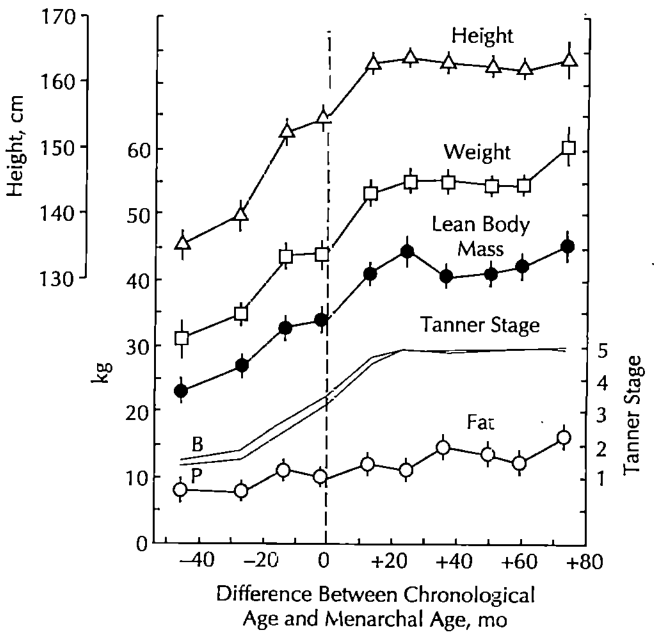

Fig 2.—*Data on stature, weight, lean body mass, fat, and Tanner stage for pubic hair (P) and breast (B) for 113 normal girls, plotted according to the difference between chronological age at measurement and menarchal age. Vertical bars indicate SEMs.*

Figure 3 shows the steady progression in midarm circumference and in hip circumference prior to menarche and a further increase in hip circumference after menarche. Hip circumference shows a greater relative increase than does arm circumference. However, both the percentage of body fat and average skinfold thickness exhibited relatively little change in this group of girls. Skinfold measurements were made on the upper portion of the body; in retrospect, it would have been of interest to include lower-body sites.

Additional measurements are shown in Fig 4. The ratio of sitting height to standing height appears to undergo a prompt increase following menarche. However, this may be confounded by the increase in gluteal fat (see hip circumference, Fig 3) and thus cannot be taken as accurately portraying the ratio of trunk length to leg length.

It is of interest that hand span achieves its maximum value at the time of menarche, while stature continues to increase for an additional year (Fig 2). Handgrip strength shows a progressive increase during the premenarchal years, reaching a maximum about 1 year after menarche.

Further measurements are shown in Fig 5. Both the ratio of lean body mass to height and the ratio of weight to the square of height (body-mass index) show a steady progression throughout the perimenarchal years covered by this study. There is no discernible effect on these indexes from the advent of menarche per se.

The abdomen-hip circumference ratio, shown in the lower portion of the graph, is an index of body fat distribution. Adult men tend to have a higher ratio than women, whereas, in preadolescent children, there is no sex difference.[6] The data in Fig 5 show that the abdomen-hip ratio progressively declines as menarche approaches, so that acquisition of the female adult fat distribution pattern has been partly achieved by the time of menarche. Hammer et al[7] have related the premenarchal decline in the abdomen-hip ratio to the stage of pubertal development.

Figure 6 shows a group of measurements having to do

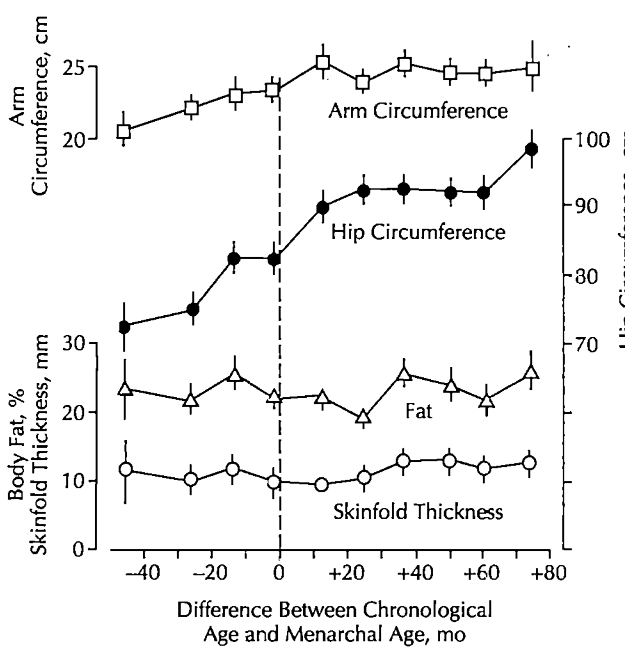

Fig 3.—*Data on midarm circumference, hip circumference, percentage body fat, and average skinfold thickness for 113 normal girls, plotted according to the difference between chronological age at measurement and menarchal age. Vertical bars indicate SEMs.*

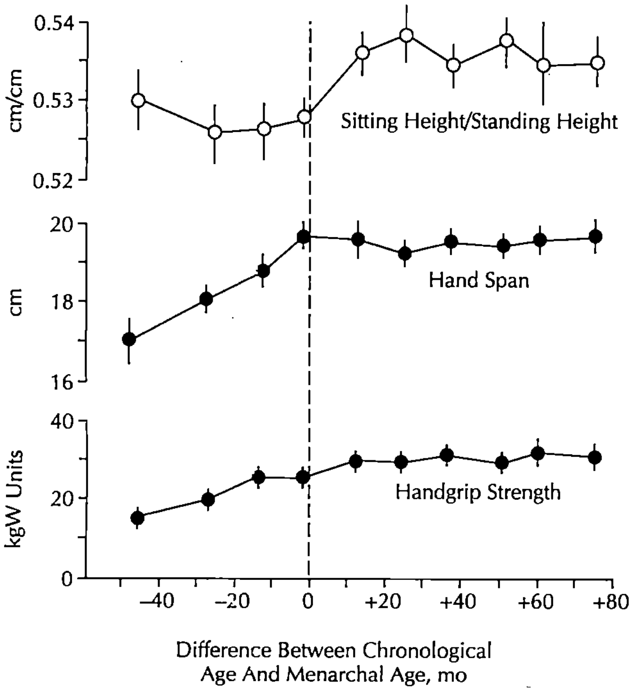

Fig 4.—*Data on ratio of sitting height to standing height, hand span, and handgrip strength for 113 normal girls, plotted according to the difference between chronological age at measurement and menarchal age. kgW indicates kilogram weight. Vertical bars indicate SEMs.*

with the skeleton. Metacarpal cortex size, both cross-sectional area at midshaft and total cortex volume calculated as described in the "Methods" section, undergo increases prior to menarche, and this bone continues to grow for some time after menarche. Bone age, as estimated from roentgenograms of the left wrist, pursues its expected course. In the group of 15 girls closest to menarche (Table), mean bone age was 153 months (±4.3, SEM), which is

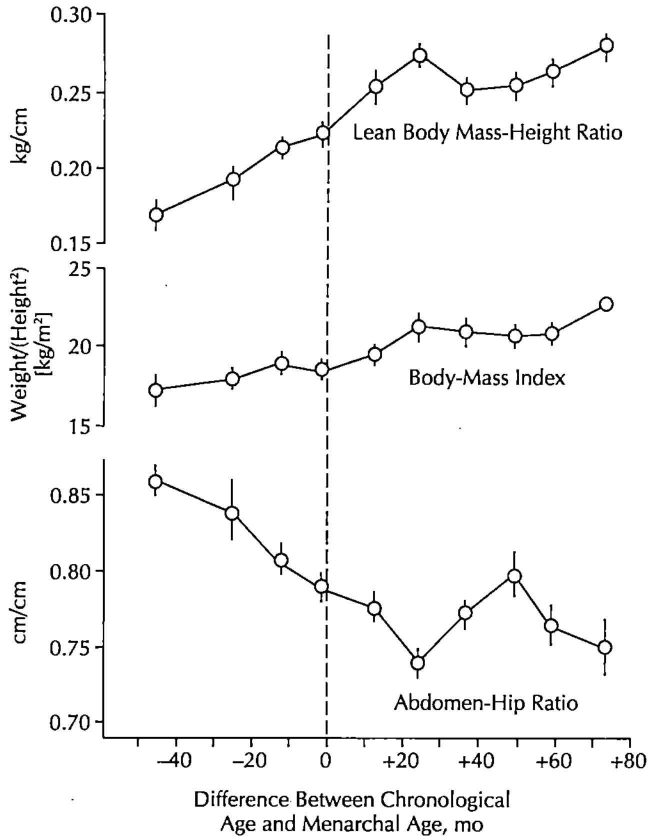

Fig 5.—*Data on ratio of lean body mass to height, body-mass index, and abdomen-hip circumference ratio for 113 normal girls, plotted according to the difference between chronological age at measurement and menarchal age. Vertical bars indicate SEMs.*

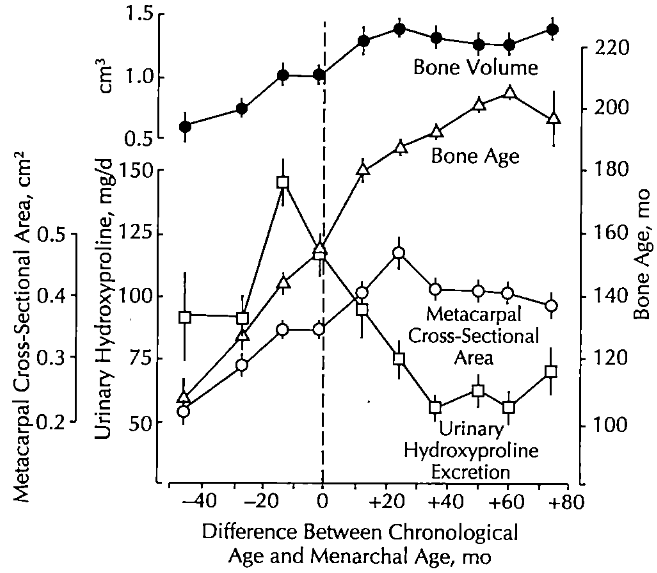

Fig 6.—*Data on metacarpal cortex bone volume, metacarpal cross-sectional area, bone age, and 24-hour urinary hydroxyproline excretion for 113 normal girls, plotted according to the difference between chronological age at measurement and menarchal age. Vertical bars indicate SEMs.*

identical to their mean chronological age (153±4.2 months). Translated into years, mean bone age (12.75 years) at menarche is the same as mean chronological age (12.8 years) at menarche for the entire group of 113 girls.

Hydroxyproline excretion represents an interesting departure from the other items shown in the figures, in that there is a significant rise about a year in advance of menarche and then an eventual fall to levels well below those of the late childhood years. This suggests that bone turnover and/or remodeling is proceeding at a relatively rapid rate in the immediate premenarchal years. A similar finding has been reported by Togo and Togo[8] and by Yoneyama and Nagata.[9]

COMMENT

Previous workers have documented the fact that menarche follows shortly after the peak of the height velocity curve[10]; hence, peak height velocity is more closely related to menarchal age than to chronological age. Shock[11] then showed in a longitudinal study that changes in basal oxygen consumption, pulse rate, and blood pressure occurred in close association with menarche.

The data presented in the present study make it evident that the perimenarchal years are associated with an array of changes in body size and composition, in skeletal size, and even in the distribution of body fat. Many of these changes are temporally related to menarche, so it is obviously impossible to designate any of them as a "trigger" for this event. Indeed, those features generally associated with androgen effects, such as increases in lean body mass and handgrip strength, exhibit perimenarchal changes fully as great as those ascribed to estrogen effects, such as the abdomen-hip ratio, body fat acquisition, and breast development. As noted earlier, the years preceding menarche show a greater absolute increase in lean weight than in body fat. Young and her associates,[12] who estimated body composition by the method of tritium dilution in a group of perimenarchal girls, found the premenarchal increment in lean body mass to be roughly equal to the increment in body fat; urinary creatinine excretion (an index of muscle mass) also increased. The percentage of body fat showed a modest increase. These authors also noted that the changes in body composition were better related to physiological than to chronological age.

The possible role of body fat in initiating menarche has been in the minds of students of the adolescent process ever since this hypothesis was proposed some years ago. Strangely, those who were attracted to this hypothesis overlooked the fact that Frisch and her associates[13,14] did not perform body composition assays or even measure skinfold thickness but rather calculated body fat from height and weight. While it is true that female adolescence is associated with an increase in body fat content, both our data (Fig 2) and those of Young et al[12] clearly show that there is also an increase in lean weight at this time of life, and the other figures indicate that a number of anatomical changes accompany female puberty. In the light of these many changes, body fat content cannot be singled out as the prime mover for the advent of menarche.

Garn et al[15] collated data on triceps and subscapular skinfold thickness recorded in three large-scale nutrition surveys. In comparing premenarchal and postmenarchal girls of the same chronological age, they found a wide range of values, the frequency distributions being strongly skewed to the right. While the mode of the distribution was greater for the postmenarchal girls in each of the age categories, the range of values, 2 to 30 mm, was so large as to lead the authors to conclude that there is "no threshold of fatness that is critical for menarche."

The variety of events that accompany the advent of menarche strongly suggests the existence of a central control mechanism, perhaps in the hypothalamus, which sets in motion and then coordinates the multiplicity of perimenarchal events. The documented premenarchal increases in gonadotropin blood levels, including the occurrence of nocturnal surges, increase in the amplitude of daytime spikes, and a heightened luteinizing hormone response to luteinizing hormone releasing hormone,[16] are in keeping with this hypothesis, which gains credence from the fact that the magnitudes of all of these hormonal changes are related to the stage of pubertal development.

This study was supported by grants HD18454 and RR00044 from the National Institutes of Health.

All volunteers and parents gave verbal and written consent after all procedures were explained oraly and in a written consent form. The project was approved by the University of Rochester Research Subjects Review Board.

The expert assistance of Cheryl Porta and Kathy Morris is greatly appreciated.

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Indications of Early Obesity in Low-Income Hmong Children

John H. Himes, PhD, MPH; Mary Story, PhD; Kathleen Czaplinski, MS, RD; Elizabeth Dahlberg-Luby, MS

- ***Objective.*—To determine if there is evidence of obesity in low-income Hmong children.**

***Design.*—Cross-sectional survey.**

***Setting.*—Women, Infants, and Children clinics in Minneapolis, Minn.**

***Participants.*—271 US-born Hmong children, ages 1.00 through 4.99 years.**

***Selection Procedures.*—Consecutive sample of all Hmong children seen in two clinics between September and December 1989.**

***Interventions.*—None.**

***Measurements/Main Results.*—Heights and weights were measured and converted to National Center for Health Statistics *z* scores of weight for age, height for age, and weight for height. Relative to National Center for Health Statistics reference data, mean height-for-age *z* scores decline progressively after age 2 years to −1.2 *z* at age 4.5 years. Mean weight-for-height *z* scores exceeded the National Center for Health Statistics reference significantly at ages 3 and 4 years, and there was more than a fourfold excess of Hmong children beyond the 95th percentile in weight for height at these ages.**

***Conclusions.*—There is evidence of early obesity in Hmong children, an ethnic group heretofore considered to be a low risk for obesity.**

(*AJDC.* 1992;146:67-69)

Southeast Asian children in the United States typically have presented with very low weight for age and height for age relative to the National Center for Health Statistics (NCHS) reference data.[1-4] Previous studies have included children who had spent some or all of their lives in Southeast Asia, where poor nutritional or socioeconomic conditions may have played important roles in determining their growth patterns.[1,3,4] Recent data regarding growth status of Southeast Asian children born and residing in the United States have indicated some improvement since the influx of refugee children in the late 1970s.[2,5,6] Nevertheless, the available data still indicate the pattern of growth of Southeast Asian children differs from that of the NCHS reference data. Relative to these reference data, Southeast Asian children are small (low weight for age and low height for age), with height for age progressively declining after age 6 to 9 months. Weight for height typically has approximated the NCHS median.

Recently, there have been anecdotal reports of apparent obesity in Hmong children at the clinics of the Supplemental Food Program for Women, Infants, and Children (WIC) and at community health care clinics operated by the Minneapolis (Minnesota) Health Department. These clinics serve a considerable population of low-income Hmong and other Southeast Asian children. Because of the apparent conflict of these clinical reports with the published record, we assessed the growth status of Hmong preschool children attending local WIC clinics.

Since 1975, almost 1 million refugees from Southeast Asia have resettled in the United States, representing diverse ethnic groups (ie, Vietnamese, Chinese-Vietnamese, Cambodians, Laotian, Mein, and Hmong).[7] Minnesota ranks in the top five states in which Southeast Asians have resettled. For the 38 900 Southeast Asian refugees in Minnesota, ethnic composition is as follows: 44% Hmong (from rural Laos), 24% Vietnamese, 17% Cambodian, and 15% Laotian (oral communication, Ann Damon, Refugee Resettlement Program, Minnesota Department of Human Services, May 1991). Approximately 85% of all Southeast Asian refugees in Minnesota are located in the Minneapolis–St Paul area. Virtually all of the Hmong in Minnesota reside in the Twin Cities.

The children included in this study were all enrolled in the WIC program in Minneapolis. All WIC participants in Minnesota have household incomes of less than 185% of poverty levels. In Minnesota, WIC provides children with iron-fortified formula throughout the first year of life, and baby cereal and infant juice from ages 6 to 12 months. After age 12 months, supplemental food includes milk or cheese, iron-fortified cereal, eggs, dried beans, and juice. The two WIC clinics with the highest proportion of Southeast Asian clientele were selected for the study.

SUBJECTS AND METHODS

Heights and weights were measured in all Southeast Asian children seen at the two clinics between September 1989 and December 1989. Anthropometric measurements were collected on 345 children between the ages of 1.0 and 4.99 years, all of

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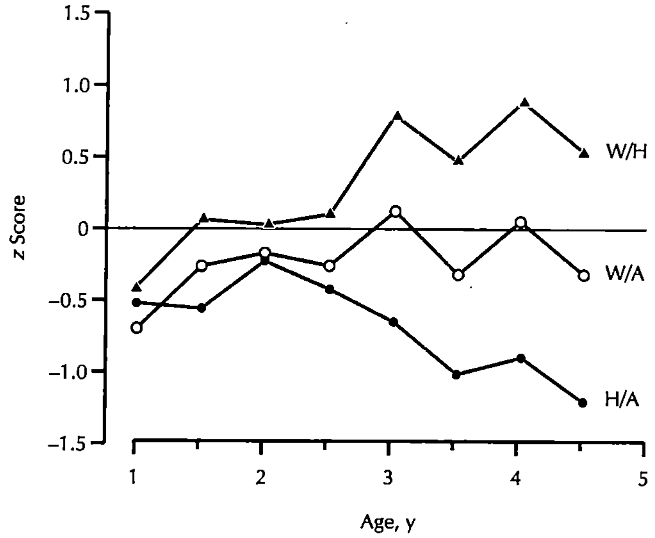

Mean z scores of Hmong children for height for age (H/A), weight for age (W/A), and weight for height (W/H).

whom were born in the United States. Information was gathered concerning ethnic group, sex, and date of birth. Ethnicity was determined by surname, language spoken, and mother's declaration. The sample included 271 Hmong, 36 Laotian, 12 Vietnamese, four Cambodian, and two Thai children. Specific ethnicity was not recorded for 20 Southeast Asian children. Because of their small numbers, we excluded from the analysis children whose ethnicity was unknown or other than Hmong. The resulting data comprised 271 ethnically Hmong children (134 boys and 137 girls).

Height and weight measurements were performed by four WIC staff trained in recommended anthropometric protocols[8] by one of the authors (J.H.H.). Length was measured until age 24 months, and stature was measured thereafter. Weight was measured with a pediatric balance (Detecto Scale Co, Long Island, NY) for children younger than age 2 years and with a beam balance for children aged 2 years and older. The anthropometry was compared with the NCHS reference data to yield z scores specific to sex and age for weight for age, height for age, and weight for height.[9,10] These z scores describe the relative distances from the reference medians in terms of SD units, with expected means of 0. We have combined the findings for boys and girls due to the small sample sizes and in the absence of systematic sex differences.

RESULTS

The mean z scores of the Hmong children are presented in the Figure by half-year age groups. The anticipated pattern of progressively smaller mean z scores for height with increasing age is evident in this sample, with a statistically significant negative rate of decrease of −0.24 for height z per y ($P<.001$). Mean weight, however, did not decline during the same period. Consequently, mean weight-for-height z scores tend to increase so that at ages 3 to 4 years these very short children exceed the NCHS medians for weight for height by almost three fourths of an SD. The mean weight-for-height z scores at ages 3.0, 3.5, and 4.0 years are significantly larger than 0 ($P<.05$). The age-associated increase in mean weight-for-height z scores is statistically significant, and the rate of increase from the resulting regression slope is 0.25 z per y ($P<.001$).

A corollary of the pattern of age-group means can be seen in the Table, which presents the distributions of Hmong children according to selected percentile cutoff points for the NCHS reference data. The excess proportions of children beyond the expected 5% below the fifth percentile for height for age document the anticipated shortness in these children. Particularly striking, however, are the more than fourfold excesses of children at ages 3 and 4 years above the 95th percentile for weight for height.

Distribution of Hmong Children According to NCHS Percentiles*

		Hmong Children, %		
Age Group, y	**No.**	**<5th Percentile**	**5th-95th Percentile**	**>95th Percentile**
Weight for age				
1	72	9.7	87.5	2.8
2	76	10.5	85.5	3.9
3	69	5.8	88.4	5.8
4	54	16.7	70.3	13.0
Height for age				
1	72	12.5	84.7	2.8
2	76	9.2	84.2	6.6
3	69	21.7	72.5	5.8
4	54	24.1	70.3	5.6
Weight for height				
1	72	4.2	87.5	8.3
2	76	3.9	90.8	5.3
3	69	0.0	76.8	23.2
4	54	3.7	74.1	22.2

*Percentages totaling more or less than 100 within age categories are due to rounding. NCHS indicates National Center for Health Statistics.

COMMENT

Our findings of low height for age and low weight for age compared with the NCHS reference data are similar to those of other studies on Southeast Asian preschool children in the United States.[1,2] Nevertheless, in both previous studies, weight for height closely approximated the NCHS median. In our data, weight-for-height status increased significantly with age, and significantly exceeded the median, suggesting that overweight or obesity is a problem after age 3 years.

The upper percentiles of weight for height are used frequently to define those individuals who are overweight or obese, although we cannot be certain that the excess weight for height seen in the Hmong children represents excess adiposity, and not additional lean tissue. At this age, however, such variation in fat-free mass would be highly unusual,[11,12] and the clinical impressions of these children as "fat kids" support the more obvious presumption of excess fat.

We do not know if these early excesses in weight for height continue after age 4 years, or if the reported patterns represent local phenomena. Our sample of Southeast Asian children included too few who were of other ethnic backgrounds to determine if the other children have the same weight-for-height patterns. Our study is cross-sectional, and one would prefer to follow up children prospectively to ensure that the age patterns are not due to the vagaries of sampling, including cohort effects. Nevertheless, we believe the data are sufficient to support a conclusion of early obesity in this group. Skinfold measurements or other measures of body fat, of course, would help confirm these conclusions.

We are unaware of such early indications of obesity being reported previously for the Hmong or other Southeast Asian children in this or any other country. Baldwin and Sutherland[2] looked at growth patterns of first-generation Southeast Asian infants, but only up to age 18 months. In our study, overweight did not become apparent until age 3 years. In the study by Dewey et al,[1] data were collected on Southeast Asian children (ages 2 through 6 years) from 1980 through 1984, with the mean length of time in the United States being only 21.8 months. In addition, only 7% of the Southeast Asian children living in California were born in the United States. We have speculated that the previously unreported obesity seen in our study represents an unwelcome response to acculturation in this country.

The Hmong, as with other Southeast Asian refugees, have undergone drastic changes in their traditions, customs, and life-styles. The Hmong, in particular, underwent a dramatic transplantation from living in rural, isolated, mountainous regions of Laos to living in a major urban area within the United States. We know of no data documenting relationships between changes in life-style factors among Southeast Asian children and obesity in young children.

Recent studies on Southeast Asian adolescents[13,14] have shown a gradual shift away from native foods toward preference for American foods. Interestingly, Hmong school children in Minneapolis were more likely to adopt American food preferences and practices than were Cambodians, and were particularly more likely to do so than were the Vietnamese. When asked if they would rather eat American food or their native food, only 38% of the Hmong children preferred eating their native food, compared with 91% of the Vietnamese and 85% of the Cambodians.[14] Unfortunately, we have no information on dietary preferences and food choices of adult Hmong living in the United States.

We believe our results may have identified an emerging pediatric problem in a group heretofore considered to be at low risk for obesity. Further research is needed to document the prevalence of obesity using more specific measures of body fatness. In addition, acculturation changes in food consumption and exercise patterns, and possible relationships with weight status, should be studied.

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The Validity of Continuing Developmental Follow-up of High-Risk Infants to Age 5 Years

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• We conducted a study to determine whether performance on developmental tests at age 5 years could predict academic achievement at age 8 years. As part of a longitudinal developmental surveillance project, 179 children at risk due to perinatal complications who had passed developmental screening through age 2½ years and 50 comparison children underwent an extensive prekindergarten psychoeducational test battery at age 5 years and took the Iowa Tests of Basic Skills at age 8 years, if they had reached the third grade. The mean Iowa Tests of Basic Skills score was significantly lower for those children who were "flagged" on the prekindergarten psychoeducational test battery ($t = 5.39$). Preacademic, rather than developmental, items appeared to be the best predictors. However, the prekindergarten psychoeducational test battery correctly predicted low achievement or grade retention in only 58% of cases. Its sensitivity was 0.45 and its specificity was 0.85. No significant difference was noted between group Iowa Tests of Basic Skills mean scores for the high-risk or comparison group. When low achievement and failure to reach the third grade were combined, prevalence of "failure" was higher for the high-risk group (31% vs 24%). The only perinatal variable predictive of low achievement was neonatal seizures. In summary, because the ability to predict future academic achievement at age 5 years is limited, routine developmental testing for symptom-free preschool children is not warranted. High-risk infant follow-up programs should focus on the first several years of life.

(*AJDC.* **1992;146:70-75)**

Developmental surveillance of children at risk due to low birth weight or other perinatal complications is costly and labor-intensive. There is little disagreement that certain risk factors (eg, hypoxic-ischemic encephalopathy and grade IV intraperiventricular hemorrhage) are likely to result in major disabilities, that these problems can and should be detected during infancy, and that intervention programs mandated through federal and state statutes should be made available to affected infants and their families as early as possible. However, subtle sequelae of early central nervous system injury, such as learning and attentional problems that may not be manifested or detectable until a child reaches school age, pose more difficult questions to those responsible for monitoring the development of "graduates" of the neonatal intensive care units. Are children with biologic risk factors more likely to manifest learning difficulties than those without such difficulties? Can such difficulties be detected before entry into school?

In answer to the first question, accumulating reports from longitudinal studies of outcomes at age 5 years and beyond of biologically at-risk infants indicate that, as a heterogeneous group, overall cognitive abilities generally fall within the normal range.[1-5] However, a pattern of underachievement clearly has emerged, according to investigators who have studied these children in depth. They have discovered specific learning problems and a higher-than-expected rate of school failure requiring special educational assistance.[6-13] Vohr and Garcia Coll,[14] for example, found 28% of neurologically normal 1-year-old very-low-birth-weight infants functioning below grade level at school age or receiving special resource help. In a study by Sell et al,[15] 48% of neonatal intensive care unit graduates were having "school problems" despite mean scores within the normal range on the McCarthy Scales of Children's Abilities. Factors such as delayed language skills,[16] weaker visual-motor and perceptual function,[5,4] and difficulties with quantitative tasks[4] may account for the unexpectedly poor school performance by some high-risk children.

From these studies, it might be concluded that, despite justifiable optimism regarding general cognitive outcomes, children with perinatal risk factors, such as low birth weight, asphyxia, or meningitis, who are found to be free of major neurologic abnormalities remain at risk for learning disabilities.

The purpose of our study was to determine whether later learning problems could be predicted reliably in the preschool years among biologically at-risk children. If so, it could be asserted that close developmental surveillance of this population at least up to entry into school is warranted.

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Table 1.—Neonatal Risk Factors That Qualify a Child as High Risk and Percentage of Children With Each Factor (Not Mutually Exclusive) (N=179)

Risk Factor	% With Factor
Birth weight≤1500 g	22
Respiratory distress syndrome	46
Bacterial meningitis	1
5-min Apgar score ≤6	27
Hypoglycemia (serum glucose level ≤2.2 mmol/L on two measurements)	9
Neonatal seizures	6
Hypotonia at discharge from nursery	1
Ventilatory assistance for >2 h	39
Other	9

Table 2.—Subtests Used in Psychoeducational Battery at Age 5 Years

Test Instruments	Functions Assessed
Verbal ability	
Boston Naming Test[34]	Expressive language: verbal labeling and word retrieval in naming drawings of common objects
Token Test[35]	Receptive language: understanding and execution of verbal directions
Vocabulary (WPPSI)[36]*	Expressive language: oral vocabulary and description of word meaning
Sentences (WPPSI)[36]	Immediate verbal memory for meaningful information
Auditory association[37]	Understanding and explaining verbal analogies
Perceptuomotor ability	
Block patterns[38]	Visuospatial perception and visuoconstructive ability in three-dimensional block building
Developmental Test of Visual-Motor Integration[39]	Visuospatial perception and graphomotor skill in copying geometric designs
Recognition-discrimination[40]	Visual scanning, visual perception, and shape matching (without motor demands)
Corsi cubes[41]	Spatial memory span in recalling positions of randomly arranged blocks
Preacademic learning	
Letter identification[42]	Recognition and naming of uppercase and lowercase letters
Segmenting Test[43]	Ability to divide words into component phonemes
Number concepts[42]	Counting specified numbers of objects
Number questions[44]	Solving oral arithmetic problems
Behavior	
Child behavior checklist[45]	Parent report of internalizing and externalizing behavior problems
Home environment	
Home Environment Questionnaire[46]	Report of objective characteristics of child's psychosocial environment, including life change events, affiliation with family, influences leading to aggression, and socioeconomic status

*WPPSI indicates Wechsler Preschool and Primary Scale of Intelligence.

SUBJECTS AND METHODS

Of 260 children with perinatal complications (Table 1) whose development was monitored in a statewide high-risk infant follow-up program[17] to age 5 years, 194 (75%) were tracked up to 8 years of age. Fifteen subjects had incomplete data, leaving 179 for analysis. Of this group, 143 (80%) were in the third grade and took the Iowa Tests of Basic Skills (ITBS).[18] The other 36 had not yet been promoted to third grade, although they were eligible by age. The mean birth weight of the study group was 2437 g (SD, 997 g; range, 815 to 5425 g). Mean maternal education level was 13.5 years (SD, 1.9 years). Sixty-one percent of the subjects were boys.

The ITBS comprise a battery of 13 nationally administered and normed achievement tests designed to provide objective information about academic performance that constitutes a partial basis for instructional decisions for individual pupils. Results are reported as percentile ranks for individual skill areas (eg, math and reading) and a basic composite battery that includes vocabulary, reading, spelling, and math concepts, problems, and computation. For data analysis and ease of interpretation, we converted these percentile rank scores into normalized standard scores for which the population mean (of all students taking the ITBS) is 50 and the SD is 10. We used Iowa rather than national ITBS norms for analysis.

The study cohort underwent an extensive prekindergarten psychoeducational test battery at age 5 years that assessed verbal, perceptual-motor, and preacademic skill (eg, number concepts and letter recognition) attainment (Table 2). Behavior and home environment were assessed as well. Details of this phase of the study and results were reported previously.[2] This group had previously passed developmental screening through age 30 months and was thought to be free of major cognitive or motor impairments.[17]

Fifty comparison children with normal perinatal histories and matched for age and maternal education levels to the high-risk group underwent the same 5-year test battery and took the ITBS as well. Their scores were compared with those of the high-risk group.

The ITBS scores were related to perinatal risk factors, psychosocial factors, and parent reports of behavior through correlational analyses. Predictive validity of the test results at age 5 years in the identification of high-risk children with low achievement at age 8 years was examined with two-by-two contingency tables based on fixed a priori test cutoffs and on discriminant analysis. Student's *t* tests were used to compare achievement test results between the high-risk and comparison groups.

RESULTS

Whereas the high-risk group performed significantly below the comparison group on the prekindergarten psychoeducational test battery at age 5 years, no differ-

Table 3.—Differences in Mean Psychoeducational Test Scores at Age 5 Years and in Mean Iowa Tests of Basic Skills Composite Scores at Age 8 Years Between High-Risk and Comparison Children*

	Test Scores by Groups		
	High-Risk	Comparison	P
Age 5 y	45.9 (9.2)	50.6 (8.5)	.001
Age 8 y	50.4 (8.2)	51.1 (8.1)	NS

*Values are mean (SD). NS indicates not significant.

ence was noted between these two groups on achievement scores (ITBS) at age 8 years (Table 3). Furthermore, no significant differences were noted between the groups on specific ITBS subtests of vocabulary, reading, spelling, or math concepts. This comparison does, however, exclude children who were not yet in third grade, although they were eligible by age, which is the group most likely to have experienced early academic problems.

When ITBS results were compared for high-risk children who were "flagged" on verbal, perceptual-motor, preacademic, and overall scores from the 5-year battery (ie, scored more than 1 SD below the mean) vs children not flagged, the flagged group showed consistently lower performance in the three test areas as well as overall (Table 4). In a multiple regression model in which the independent variables were verbal, perceptual-motor, preacademic, and composite scores from the 5-year battery and the dependent variables were ITBS composite, reading, and math scores, preacademic scores accounted for most of the variance in the ITBS composite ($R=.47$, $R^2=.22$, $P<.0001$) and reading ($R=.39$, $R^2=.15$, $P<.0001$) scores. However, perceptual-motor scores at age 5 years appeared to be most important for math achievement at age 8 years ($R=.40$, $R^2=.16$, $P<.0001$).

Although the group of children who were flagged at age 5 years did more poorly on achievement tests at age 8 years than those who were not flagged, an important question for the clinician or for a high-risk infant follow-up program is the ability of developmental or academic readiness tests at age 5 years to predict poor achievement in school, so that early remedial or preventive services can be implemented for the individual child. Table 5 summarizes the ability of the 5-year battery to identify individual children who would do poorly on achievement tests at age 8 years (ie, achieve a score on the ITBS more than 1 SD below the mean) or would not yet be in the third grade, although they were eligible by age. Predictions of "pass" or "fail" were based on a fixed a priori cutoff (more than 1 SD below the mean) on the 5-year overall score. With use of the 1-SD cutoff on the overall 5-year battery score as the predictor, correct identification at age 5 years of which children would do well or poorly at age 8 years occurred in 73% of cases ("hit rate"). Five-year-old children who would not have problems were correctly identified 85% of the time (specificity), but those who would manifest problems were correctly identified in only 46% of cases (sensitivity). Therefore, there was considerable underidentification, with a false-negative rate of 53%. The false-positive rate, however, was quite low. When a child was flagged at age 5 years, there was a 58% chance that he or she would do poorly in school based on the fixed cutoff (predictive test positive). In other words, he or she was almost as likely to do well as not to do well. Conversely, if the child did well at age 5 years, there was a 78% chance that he or she would perform satisfactorily in the third grade as well (predictive test negative).

Table 4.—A Comparison of Iowa Tests of Basic Skills (ITBS) Scores for High-Risk Children Who Were "Flagged" on 5-Year Tests vs Those Who Were Not*

5-y Test Results	ITBS Scores at Age 8 y	
	Mean	P
Verbal		
Flagged	46. 0 (8.1)	.002
Not flagged	51.5 (8.6)	
Perceptual-motor		
Flagged	45.1 (8.4)	.000
Not flagged	51.9 (8.3)	
Preacademic		
Flagged	44.3 (8.3)	.000
Not flagged	52.4 (7.9)	
Composite		
Flagged	43.4 (8.3)	.000
Not flagged	52.2 (7.9)	

*According to Iowa norms, mean score is 50 and SD is 10. Values are mean (SD).

Table 5.—Properties of 5-Year Tests or Their Ability to Predict a Pass or Failure at Age 8 Years for an Individual High-Risk Child*

5-y Test Results	ITBS Results		Total
	Pass	Fail	
Pass	26	19	45
Fail	30	104	134
Total	**56**	**123**	**179**
Sensitivity	0.46		(0.39-0.53)
Specificity	0.58		(0.80-0.90)
False-negative rate	0.54		(0.47-0.61)
False-positive rate	0.15		(0.10-0.20)
Positive predictive value	0.58		(0.51-0.65)
Negative predictive value	0.77		(0.71-0.83)
Prevalence of ITBS failure	0.31		(0.24-0.38)
Accuracy of 5-year tests	.73		(0.66-0.79)

*A failure on the 5-year test is a score greater than 1 SD below the mean; a failure at age 8 years is an Iowa Tests of Basic Skills (ITBS) score greater than 1 SD below the mean *or* failure to reach the third grade, although eligible by age. (Values in parentheses are 95% confidence limits).

Because a priori test combinations or cutoffs may not be ideal for maximization of predictive accuracy, a discriminant analysis was performed with the use of all of the 5-year cognitive and behavioral tests (Table 2) from 179 children as predictors of low ITBS scores at age 8 years or failure to reach the third grade. This technique was used to set an upper limit on the possible accuracy of 5-year predictors rather than to develop a prediction model (which is beyond the scope of this study). Some modest improvements in prediction were found: specificity increased to 93%, the false-positive rate decreased to 7%, and overall accuracy increased slightly to 79%; otherwise, variables, including sensitivity, were essentially unchanged.

In an examination of the 5-year test results of those children for whom ITBS results were available vs those who were unavailable for follow-up, the latter group had performed significantly below the former ($t[2,247]=3.03$, $P<.01$), indicating that the ITBS scores reported above may be an overestimate of the overall achievement of children with high-risk birth histories. Although the conclusions regarding the ability of tests administered at age 5 years to predict later school achievement should not be invalidated by this observation, some children with serious developmental problems were undoubtedly missed. However, there were no differences in maternal education levels between those tracked to age 8 years and those unavailable for follow-up, suggesting that there were not major socioeconomic differences between the groups.

Because the ITBS are not administered routinely to children below the third-grade level, achievement scores were unavailable for children for whom follow-up information was obtained (eg, domicile and grade level) but who were not yet in the third grade, although they were eligible based on age. Their 5-year scores in all areas were significantly below those of children who were in the third grade ($t[2,180]=3.15$, $P<.01$). Either these children had been retained in one of the early grades or poor performance at age 5 years had swayed parents to delay entry into kindergarten for their child or to seek an alternative placement for that academic year, such as a preschool or special kindergarten. In an evaluation of the predictive validity of testing at age 5 years (Table 5), "failure" at age 8 years included the child's not being in the third grade as well as poor performance on the ITBS. The reason that children not in the third grade were included in the sensitivity, specificity, and prevalence analyses was to balance the possibility that the third graders represented the better academic performers among the high-risk subjects. While including these children as failures at age 8 years, thereby increasing the prevalence of "failure", does not affect sensitivity or specificity, it does influence estimates of predictive value for the 5-year tests. Higher prevalence rates result in higher positive predictive values and lower negative predictive values. Thus, our results, based on the higher estimate of prevalence of "failure" at age 8 years, represent a liberal estimate of positive predictive value. If the prevalence were lower than our 0.31 value, the positive predictive value would be lower than 0.58, strengthening our argument about the limitations of accurately predicting future school problems at age 5 years.

The prevalence estimate of 0.31 is not unusually high when compared with values reported in other longitudinal studies[19] or national surveys[20] that have included identification of both mild and severe learning problems. We are identifying problems in academic achievement and class placement ranging from mild to severe, rather than diagnosing a specific learning disorder (eg, developmental dyslexia). The prevalence rate for failure in our non–high-risk comparison group utilizing ITBS scores (more than 1 SD below the mean) or grade retention below the third grade was lower, at 0.24.

The influence of perinatal risk factors (Table 1), parental reports of behavior at age 5 years, socioeconomic status, and home environment on ITBS scores was explored by correlational analyses. None of these factors was significantly related to ITBS results. Furthermore, birth weight as a continuous variable was not significantly correlated with ITBS scores. Because the high-risk children with the poorest academic achievement were not yet in third grade and therefore had not taken the ITBS, their school performance could not be examined through these correlational analyses. To include the entire high-risk sample, an attempt was made to develop a logistic regression model using perinatal variables to predict "success" or "failure" at age 8 years. Overall, predictive accuracy did not significantly exceed chance levels, and only one perinatal risk factor, neonatal seizures, was associated with increased relative risk (1.9) for school problems after adjustment for the effects of other variables.

COMMENT

Of major importance for pediatric practice and public policy is the effectiveness of committing considerable resources to extensive evaluation of high-risk children beyond infancy. While relatively inexpensive techniques may be effective in the identification of major developmental problems for the very young child, such approaches have been found to be unsuccessful in revealing learning problems among preschool children.[21,22] Assessments of specific areas of function, such as language or perceptual-motor skills, require more time and expertise than screening procedures such as the Denver Developmental Screening Test,[23] despite their potential for greater validity. However, there must be evidence of the substantially greater usefulness of extensive evaluations if they are to be routinely employed for populations at risk.

The question posed herein was whether detailed evaluations of developmental function of high-risk children at age 5 years could successfully identify children who would perform poorly on achievement tests at age 8 years. Indeed, the group of children who did poorly at age 5 years attained significantly lower scores on third-grade achievement tests than those who had done well.

Prediction for an individual child, although more often correct than incorrect, was problematic. A child who did poorly on tests at age 5 years was only slightly more likely to be a poor achiever at age 8 years than an adequate achiever (predictive test positive). Thus, enlisting special educational supports for such a child at age 5 years with little more than a 50% chance of school difficulty does not seem justifiable, especially if there are no concerns on the part of parents or teachers. Because preventive educational programs for preschool children deemed at risk for school problems were not widely available in Iowa at the time of this study, it is unlikely that remedial work ameliorated deficiencies that were apparent at age 5 years. Therefore, intervention is not a likely explanation for adequate achievement in third grade of many children with low 5-year test scores, although some children may have been helped by giving special attention to their cognitive strengths and weaknesses.

The underidentification of future low achievers (false-negative rate [54%]) was equally disappointing. If the rationale for preschool identification of learning problems is timely intervention, the majority of children who might need such help may not be recognizable until later in school. Measures of home environment, socioeconomic status, and child's behavior were neither clinically nor statistically significantly correlated with later ITBS scores.

These results further suggest that extensive developmental evaluations at age 5 years are only moderately accurate in predicting later learning problems and may not be cost-effective.

A study of 350 children with neonatal risk factors in Finland produced remarkably similar results.[24] Excluding children with major handicaps, the investigators found that abnormal results of a neurodevelopmental examination at age 5 years to be predictive of failure on 9-year examinations and school problems in only 30% to 60% of cases. In another study, Feschbach and coworkers[25] found that only 46% to 66% of preschool children identified as likely to have future school problems actually were having problems at the end of the second grade.[25]

Although a number of studies have shown predictive relationships between preschool assessment results and later school performance, three reviews of the literature on preschool prediction of later learning problems resulted in similar conclusions that neither single measures nor sets of measures provide invariably accurate forecasts of a child's academic learning.[26-28]

Certain tests may correctly distinguish children falling at the extremes of ability but can miss children having more selective difficulties that may impede later learning. False-positive errors may result from rapid, uneven maturational changes that occur in preschool children. What appears to be a deficit at one point may not be so 12 months later. Furthermore, temperamental and behavioral characteristics of the child, the capabilities of the examiner to establish rapport, or special circumstances (the child pondering a birthday party later that day or a recent announcement of parental separation) may affect performance on tests adversely. On the other hand, in many cases, the condition (eg, reading difficulty) does not exist or the effects of brain impairment may be silent until the need arises to develop and utilize a particular skill.

In contrast to the studies cited in the introduction to this article, which report high rates of school failure among low-birth-weight infants, the mean score on achievement tests for the high-risk group in our study was not statistically different from that of the comparison group. Unlike other studies that include complete cohorts of high-risk children, this report only includes those children who passed earlier developmental and neurologic screenings through 30 months of age. Thus, this group does not include high-risk children with major cognitive and physical impairments who were identified in their first years of life and who clearly would have problems in school. It is also possible that children who were unavailable for follow-up and, therefore, were unaccounted for had higher rates of school problems.

However, when failure to reach third grade was considered, the high-risk group had a failure prevalence rate of 31% vs 24% for the comparison group. Still, our study suggests that the notion of lingering subtle neurologic dysfunction in high-risk children who appear to be developmentally "clean" in their preschool years applies only to a minority.

Most perinatal risk factors were not useful to predict which children would be poor achievers in the third grade, although they were highly associated with moderate to severe developmental outcomes in the first few years of life.[17] Surprisingly, even birth weight was not related to ITBS scores. Cohen et al[29] also found that early hazardous medical events were not associated with later learning problems. While some studies have demonstrated an increasingly influential effect of the environment on later performance of children with biologic risk factors,[30,31] socioeconomic status and home environment were not discriminating of poor achievement in this study, possibly because of the relative homogeneity of the sample. This homogeneity does allow a look at more purely biologic risk factors as predictors, but the value of these factors to predict long-term developmental outcomes among children without major cognitive impairment appears to be limited. This observation further weakens the rationale for continued developmental surveillance based on perinatal complications beyond the early years of life when they have more direct and immediate influence.[32,33]

From this study, we conclude that although children with perinatal complications who pass early developmental screenings may be at mildly increased risk for low academic achievement, only moderate accuracy can be achieved in identifying, before entry into kindergarten, which children will do poorly in the third grade. This makes universal evaluation for all high-risk children at age 5 years insufficiently effective to be justifiable in terms of resource allocation. Because the test battery used in our study at age 5 years approached the diagnostic level of sophistication and meets or exceeds the predictive accuracy of other studies, less extensive developmental screening would be even less rewarding.

Academic readiness screening, on the other hand, may be useful to determine whether a child is sufficiently mature and has the expected prerequisite skills to begin a successful kindergarten career. This service, however, should be available to all children and not just to those with biologic risk factors. Full diagnostic developmental assessment should be reserved for those children about whom parents, preschool teachers, or others have specific concerns regarding learning or behavior.

As neonatal, community, and state programs develop systems to track the developmental needs of young children deemed at risk, the length and methods of follow-up must depend on the yield of information useful for the identification of appropriate support services. It appears that the yield from follow-up during infancy is high, but the yield declines as children become older. Thus, until more precise methods of assessment are available for preschool children, developmental surveillance programs for children with perinatal risk factors may be well advised to concentrate their screening resources on infants and toddlers. At the same time, the general educational community must become more sensitive to the mildly increased risk of school problems among high-risk children, the need to monitor each individual child's progress closely, and the importance of intervening before a long history of failure has developed.

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Youth at Risk

Sex, Drugs, and Human Immunodeficiency Virus

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• **Adolescents and young adults are at risk for human immunodeficiency virus type 1 infection due to unprotected sexual intercourse and drug use. In 1988 and 1989, blinded surveys were conducted in 84 sexually transmitted disease clinics, 115 women's health clinics, and 19 drug treatment centers in 38 metropolitan areas. Blood specimens from 153 242 clients, aged 15 to 24 years, were tested for human immunodeficiency virus type 1 antibodies after all client identifiers were removed. In sexually transmitted disease clinics, the median rate was 0.4% among 15- to 19-year-olds, compared with 1.4% among 20- to 24-year-olds. Among heterosexual adolescents, rates in females were significantly higher than in males (Wilcoxon signed rank test). Rates in heterosexuals were highest in the northeastern and southeastern United States and in Puerto Rico. In 20- to 24-year-old male clients in sexually transmitted disease clinics who had sex with males, rates ranged from 9.7% to 55.6%. In drug treatment centers, the median rate among 20- to 24-year-old men and women was 8.3% (range, 0% to 33.3%). Rates in women's health clinics were much lower (median, 0.1%). The high rates of infection in certain groups of adolescents and young adults indicate the need for improved care, education, and outreach targeted toward those at high risk.**

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Adolescents and young adults are gaining increasing attention as a group at risk for human immunodeficiency virus type 1 (HIV-1) infection because of the high prevalence of unprotected sexual intercourse and drug use among youth. Data from national surveys of adolescents conducted in 1988 showed that 52% of females and 60% of males aged 15 to 19 years have had premarital sexual intercourse. Among 19-year-olds, 75% of women and 86% of men had been sexually active.[1,2] Regular condom use for pregnancy or sexually transmitted disease (STD) prevention is infrequent among sexually active teenagers and young adults.[3-5] Approximately one out of every 10 women aged 15 to 19 years becomes pregnant each year in the United States.[6] Adolescents and young adults have very high rates of STDs compared with older adults.[7] Few data are available regarding adolescent homosexual behavior. In the 1988 National Survey of Adolescent Males,[2] 3% of 15- to 19-year-old males reported sexual activity with other males, including anal sex, oral sex, or mutual masturbation. Studies of homosexual men indicate that homosexual activity often begins during early adolescence.[8,9]

The use of illicit drugs and alcohol is widespread among adolescents and young adults. In a survey of high school seniors, 92% reported alcohol use, 54% reported marijuana use, and 17% reported cocaine use.[10] The use of drugs, such as alcohol or crack, can impair judgment and facilitate unsafe sexual practices. In particular, exchange of sex for drugs puts youth at high risk because they often have unprotected intercourse with multiple partners. Estimates of intravenous (IV) drug use among adolescents range from 1% to 5%.[10,11] However, only high school students were sampled in these studies, and rates in out-of-school youth may be even higher.

Through July 1991, 715 cases of acquired immunodeficiency syndrome (AIDS) in 13- to 19-year-olds and 7549 cases in 20- to 24-year-olds had been reported to the Centers for Disease Control (CDC).[12] Since the incubation period between infection with HIV-1 and the onset of AIDS is lengthy, many of these young adults, aged 20 to 24 years, were infected as adolescents. Because reports of AIDS cases do not reflect the current scope of HIV-1 infection among adolescents, seroprevalence studies are useful in monitoring current trends in the epidemic. In 1988, the CDC, in collaboration with state and local health departments and other federal agencies, coordinated a sentinel surveillance system to monitor HIV-1 infection in specific subpopulations in the United States.[13] This article presents data from adolescents and young adults who attended STD clinics, drug treatment centers, and women's health clinics.

SUBJECTS AND METHODS

Study Design

The methods used for the blinded surveys at the STD clinics, drug treatment centers, and women's health clinics have been previously described.[14-16] Blinded testing provides the least biased estimate of HIV-1 prevalence. Consecutive blood specimens collected for other purposes, such as a serologic test for syphilis, were tested for HIV-1 antibodies after all client identifiers were

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removed. Specimens were tested for HIV-1 antibody using Food and Drug Administration–licensed HIV-1 enzyme immunoassays and Western blot tests. Informed consent was not required because there was no interaction with or risk to clients. At each clinic, client demographics and risk information, such as IV drug use and sexual behaviors, if available, were recorded on a CDC survey form with a precoded identification number. The survey forms and laboratory results were sent to the participating state or local health departments where they were linked by survey number using software developed at the CDC. Because all personal identifiers had been removed and it was not possible to identify an individual, clients could not be notified of their test results. However, all participating clinics offered routine HIV-1 counseling and testing or referral services, so clients who wanted to know their HIV-1 status could request testing.

In the STD clinics, blood specimens were eligible for inclusion in the survey if the clinic visit was for a new STD episode and the client had not been seen during the previous 3 months. In drug treatment centers, specimens were eligible if the client was being evaluated for admission to a drug treatment program and had used IV drugs at least once in the previous 12 months. In the women's health clinics, specimens were eligible if the client was being seen for an initial visit. Clients presenting only for HIV-1 testing or only for evaluation or treatment of an HIV-related condition and clients who were returning for a follow-up visit were excluded from the surveys.

Selection of Clinics

Metropolitan areas were selected by the CDC to participate in the surveys based on their cumulative number of AIDS cases reported to the CDC, rates of syphilis and gonorrhea, and geographic location. Individual clinics were selected by state or local health departments. Health departments selected clinics that met the following guidelines: large populations from diverse racial, ethnic, sexual orientation, and socioeconomic groups; routine medical assessment and collection of venous blood; and the ability to conduct annual surveys. The clinics enrolled in the surveys serve many low-income clients and are generally located in urban areas. Health departments generally targeted clinics that they believed would provide data useful for assisting their AIDS program planning and HIV prevention efforts.

Most STD clinics are supported by state or local health departments. Some privately funded clinics, including homosexual- or feminist-sponsored clinics, are also enrolled. The drug treatment centers are mainly methadone detoxification or methadone maintenance treatment programs. However, therapeutic communities, cocaine treatment, and drug-free outpatient programs are also included. Participating drug treatment centers are a combination of public, private, nonprofit, and for-profit centers. The women's health clinic surveys include prenatal, abortion, and family planning clinics. Most participating prenatal clinics are operated by health departments and mainly serve low-income women. The abortion clinics are generally privately supported and provide services to women from diverse socioeconomic backgrounds. The family planning clinics are operated by health departments or by private agencies.

Data Analysis

Although the clinics collect specimens from clients in all age groups, this report focuses on specimens from 15- to 24-year-olds attending the clinics from March 1988 through December 1989. Because each clinic is a unique sentinel site, seroprevalence rates were calculated separately for each clinic and were expressed as the total number of HIV-1–positive specimens divided by the total number of tests. Only STD clinics and women's health clinics that tested at least 200 specimens and drug treatment centers that tested at least 25 specimens in this age group are included in this article. Because participating clinics were not chosen as a probability sample and client demographics vary from clinic to clinic within a metropolitan area, the median and range of clinic rates are presented for metropolitan areas with multiple clinics of the same type. Rates were calculated for subgroups within an STD clinic or women's health clinic if the denominator included at least 50 specimens tested, except for males who had sex with males and IV drug users. For these groups, rates were calculated if the denominators included at least 25 specimens. The Wilcoxon signed rank test was used to compare rates between subgroups across metropolitan areas.

Table 1.—HIV-1 Seroprevalence by Clinic Type, Sex, and Age Group in Selected US Clinics, 1988 to 1989*

	Median Prevalence, % (Range)†	
	15-19 y	20-24 y
STD clinics		
All clients	0.4 (0-4.7)	1.4 (0-11.8)
Heterosexual‡		
Males	0 (0-4.4)	0.8 (0-4.8)
Females	0 (0-8.3)	0.4 (0-12.7)
Homosexual/bisexual males	. . .	30.1 (9.7-55.6)
Intravenous drug users (males and females)	. . .	0 (0-45.5)
Women's health clinics	0 (0-1.4)	0 (0-2.9)
Drug treatment centers		
Males	. . .	8.7 (0-26.7)
Females	. . .	6.7 (0-40.0)

*HIV-1 indicates human immunodeficiency virus type 1; and STD, sexually transmitted disease.

†Median prevalence is the clinic rate at which half the clinic rates are above and half are below. The range refers to the lowest and highest clinic rates.

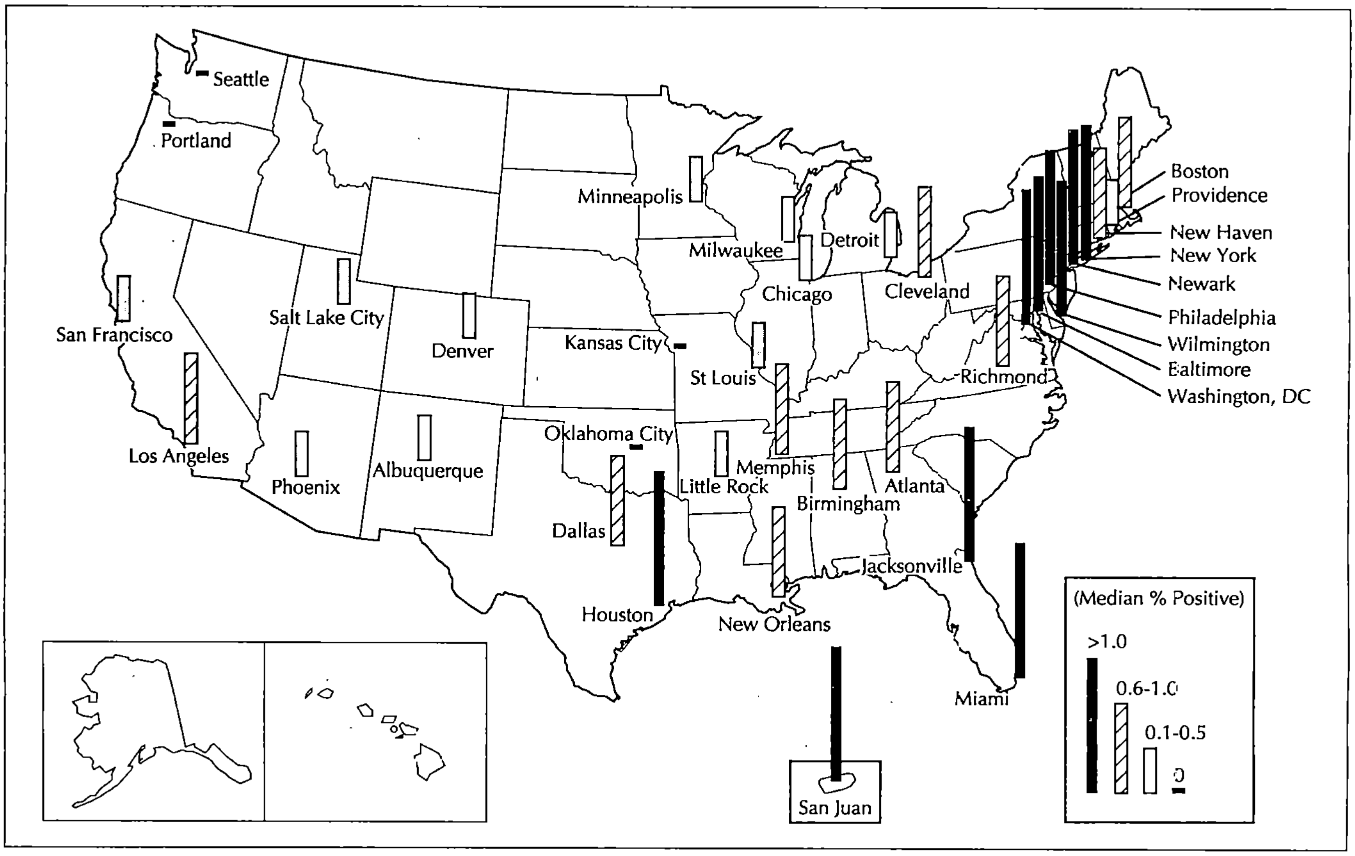
‡Includes only heterosexuals with no reported risk for HIV infection.

RESULTS

From March 1988 through December 1989, 38 metropolitan areas tested 153 242 blood specimens from 15- to 24-year-old clients. Eighty-four STD clinics, 115 women's health clinics, and 19 drug treatment centers met the minimum sample size requirement and are included in this report. Both the STD and women's health clinics serve a large number of adolescents and young adults. Overall, 43% of the STD clinic specimens and 58% of the women's health clinic specimens were from clients younger than 25 years. The drug treatment centers, however, serve an older population, with only 7% of the specimens from clients younger than 25 years. In STD clinics, most 15- to 24-year-old clients were black; in women's health clinics, the percentages of black and white clients were similar. However, in drug treatment centers only 16% of the clients were black. In STD clinics, 64% of 20- to 24-year-old clients were male compared with 54% among 15- to 19-year-old clients. In drug treatment centers, 66% of the clients were male.

STD Clinics

A total of 73 627 specimens from STD clinics were tested, and HIV-1 seroprevalence rates ranged from 0% to 9.6% among 15- to 24-year-olds, with a median rate of 1.1%. The median clinic seroprevalence rate was 0.4% in 15- to 19-year-olds and 1.4% in 20- to 24-year-olds (Table 1). Rates in young adults were significantly higher than in adolescents (Wilcoxon signed rank test, $P<.01$). Overall, 82% of 15- to 24-year-olds were identified as heterosexuals with



Human immunodeficiency virus type 1 seroprevalence in 15- to 24-year-old heterosexual clients in sexually transmitted disease clinics.

no reported risk for HIV-1. In 15- to 19-year-old heterosexuals with no reported risk for HIV-1, median seroprevalence rates were 0% for both males and females in 11 metropolitan areas. In the remaining areas, rates in female adolescents were significantly higher than in male adolescents (Wilcoxon signed rank test, $P<.01$). The maximum clinic rate was 8.3% for females and 4.4% for males. Two clinics in Miami, Fla, had exceptionally high rates in female adolescents (8.3% and 5.9%). In 20- to 24-year-old heterosexuals with no reported risk, the median clinic seroprevalence rate was 0.8% for men and 0.4% for women (Table 1). There were no significant differences between heterosexual male and female rates in the 20- to 24-year-old age group (Wilcoxon signed rank test, $P>0.05$).

The HIV-1 seroprevalence in young males who had sex with other males and had not used IV drugs was extremely high. In STD clinics that tested at least 25 specimens, the median rate was 30.1% in 20- to 24-year-olds, with a range of 9.7% to 55.6% (Table 1). Overall, 1.6% of adolescents and young adults in STD clinics reported using IV drugs. Seroprevalence rates among 20- to 24-year-old heterosexual clients in STD clinics who used IV drugs ranged from 0% to 45.5%, with the highest rate in San Juan, Puerto Rico. Clinic seroprevalence rates in 15- to 19-year-old IV drug users and in males who had sex with males could not be calculated because of the small number of individuals tested per clinic in that age group. However, all metropolitan areas combined tested a total of 269 specimens from 15- to 19-year-old males who reported having sex with males, and 44 of these individuals were HIV-1 positive.

Seroprevalence rates varied considerably between metropolitan areas and among clinics within a metropolitan area. Of the 10 metropolitan areas with the highest median seroprevalence rates among 15- to 24-year-old heterosexuals, six were located in the Northeast, three in the South, and one in Puerto Rico (Figure). Median rates in the Midwest and West were generally low. Males who had sex with males, however, had very high rates of infection across the United States, with the highest median rate in Atlanta, Ga (Table 2).

Rates among 15- to 24-year-old heterosexual clients in STD clinics ranged from 0% to 7.6% (median, 0.8%) in blacks, 0% to 6.2% (median, 0%) in whites, and 0% to 5.1% (median, 0%) in Hispanics. The differences between rates in blacks and whites and between rates in whites and Hispanics from the same metropolitan areas were not statistically significant. However, rates in blacks were significantly higher than rates in Hispanics (Wilcoxon signed rank test, $P<.05$).

Women's Health Clinics

In women's health clinics, 78 830 specimens from 15- to 24-year-olds were tested. Seroprevalence rates among 15- to 24-year-olds attending women's health clinics ranged from 0% to 1.8%, with a median clinic rate of 0.1%. Rates in 15- to 19-year-olds ranged from 0% to 1.4% (median, 0%), and rates in 20- to 24- year-olds ranged from 0% to 2.9% (median, 0%). Rates in young adults were significantly higher than in adolescents (Wilcoxon signed rank test, $P<.01$). Rates were higher than 1% among 15- to 19-year-olds in five clinics and among 20- to 24-year-olds in 11 clinics. Richmond, Va, and New York, NY, had the highest median rates among 15- to 19-year olds , and Boston, Mass, and Miami had the highest median rates among 20- to 24-year olds. Rates in 15- to 24-year-olds in women's

Table 2.—HIV-1 Seroprevalence Among 15- to 24-Year-Old Adolescents and Young Adults in STD Clinics by Metropolitan Area and Risk Exposure in Selected US Clinics, 1988 to 1989*

		Heterosexual Males†		Heterosexual Females†		Homosexual/Bisexual Males‡		Intravenous Drug Users, Males and Females‡	
	No. of Clinics	Median Prevalence, % (Range)	No. of Patients Tested§	Median Prevalence, % (Range)	No. of Patients Tested§	Median Prevalence, % (Range)	No. of Patients Tested§	Median Prevalence, % (Range)	No. of Patients Tested§
New England									
Boston, Mass	4	0.4 (0-1.0)	121-811	1.3 (0-1.5)	67-321	. . .	. . .	. . .	. . .
New Haven, Conn	1	0.7	1167	1.8	274	. . .	. . .	. . .	. . .
Providence, RI	1	0.2	440	0.4	237	. . .	. . .	. . .	. . .
Middle Atlantic									
New York, NY	5	1.6 (0-3.2)	53-311	2.5 (1.1-4.8)	80-188	32.4	34	. . .	. . .
Newark, NJ	2	1.7 (1.3-2.2)	314-868	2.0 (1.8-2.3)	112-435	. . .	. . .	14.3	28
Philadelphia, Pa	1	1.5	327	2.3	128	. . .	. . .	. . .	. . .
East North Central									
Chicago, Ill	4	0.4 (0-0.9)	122-438	0 (0-0.9)	148-270	. . .	. . .	. . .	. . .
Cleveland, Ohio	2	1.2 (0.9-1.6)	211-967	0.6 (0.5-0.7)	145-597	. . .	. . .	. . .	. . .
Detroit, Mich	4	0.5 (0-0.9)	247-1631	0 (0-0.4)	247-554	. . .	. . .	. . .	. . .
Milwaukee, Wis	1	0.7	435	0	225	. . .	. . .	. . .	. . .
West North Central									
Kansas City, Mo	1	0	313	0	229	. . .	. . .	. . .	. . .
Minneapolis, Minn	2	0.2 (0.2-0.3)	357-606	0.2 (0-0.3)	319-575	12.5	32	. . .	. . .
St Louis, Mo	2	0.3 (0-0.5)	263-729	0.1 (0-0.2)	319-509	. . .	. . .	. . .	. . .
South Atlantic									
Atlanta, Ga	3	0.8 (0.7-1.5)	398-597	0.8 (0.2-1.2)	406-666	46.2 (41.4-51.0)	51-70	1.9 (0-3.7)	26-27
Baltimore, Md	2	0.9 (0-1.9)	71-162	0.9	112	34.4	61	. . .	. . .
Jacksonville, Fla	1	2.2	360	1.8	227	. . .	. . .	. . .	. . .
Miami, Fla	2	3.2 (3.0-3.5)	440-513	9.4 (7.9-11.0)	210-290	. . .	. . .	. . .	. . .
Richmond, Va	1	0.5	382	0.8	242	. . .	. . .	. . .	. . .
Washington, DC	2	1.7 (1.1-2.2)	1183-1223	2.8 (1.9-3.6)	314-358	31.8	88	. . .	. . .
Wilmington, Del	1	0.6	354	3.1	196	. . .	. . .	. . .	. . .
East South Central									
Birmingham, Ala	1	0.5	748	0.7	588	. . .	. . .	. . .	. . .
Memphis, Tenn	1	0.6	1198	0.5	912	. . .	. . .	. . .	. . .
West South Central									
Dallas, Tex	1	0.5	207	1.1	271	. . .	. . .	. . .	. . .
Houston, Tex	2	2.3 (0.4-4.1)	219-458	1.4 (0.6-2.3)	181-341	45.0	60	. . .	. . .
Little Rock, Ark	1	0.4	280	0.4	256	. . .	. . .	. . .	. . .
New Orleans, La	2	1.1 (0.4-1.7)	247-802	0.8 (0.4-1.3)	158-545	. . .	. . .	. . .	. . .
Oklahoma City, Okla	1	0	321	0	222	. . .	. . .	. . .	. . .
Mountain									
Albuquerque, NM	1	0	511	0.4	257	. . .	. . .	2.0	51
Denver, Colo	2	0.3 (0-0.5)	260-560	0.2 (0-0.4)	237-437	24.3	37	2.6	39
Phoenix, Ariz	1	0.6	541	0.2	470	20.0	80	. . .	. . .
Salt Lake City, Utah	2	0.1 (0-0.2)	402-795	0.1 (0-0.2)	367-471	11.6	69	0.5 (0-0.9)	37-107
Pacific									
Los Angeles, Calif	8	0.6 (0.3-1.8)	208-1252	0.6 (0-4.1)	113-737	19.6 (3.1-41.8)	25-83	0 (0-0)	30-36
Portland, Ore	1	0	331	0	347	3.4	29	1.5	65
San Francisco, Calif	6	0.3 (0-0.7)	320-647	0.2 (0-1.4)	176-283	36.0	50	. . .	. . .
Seattle, Wash	3	0 (0-0.4)	328-635	0 (0-0.2)	258-784	11.8	34	0	50
Other									
San Juan, Puerto Rico	1	4.7	317	6.3	268	18.3	71	38.6	83

*HIV-1 indicates human immunodeficiency virus type 1. Median prevalence is the clinic rate at which half the clinic rates are above and half are below. The range refers to the lowest and highest clinic rates.

†Includes only heterosexuals with no reported risk for HIV infection. At least 50 specimens were tested per clinic.

‡At least 25 specimens were tested per clinic.

§For areas with more than one clinic, a range of numbers of patients is provided.

health clinics ranged from 0% to 3.2% (median, 0.3%) in blacks, 0% to 2.9% (median, 0%) in whites, and 0% to 2.0% (median, 0%) in Hispanics. Median seroprevalence rates were significantly higher in black women compared with white and Hispanic women attending clinics in the same metropolitan areas (Wilcoxon signed rank test, $P<.02$).

Drug Treatment Centers

A total of 785 specimens from IV drug users attending 19 drug treatment centers were tested. The median center seroprevalence rate among 20- to 24-year-old IV drug users was 8.3%, with a range of 0% to 33.3%. Rates in females ranged from 0% to 40%, and in males ranged from 0% to 26.7% (Table 1). The highest seroprevalence rates in 20- to 24-year-olds were in clinics in Boston and New York. Three centers in San Francisco, Calif, Los Angeles, Calif, and Seattle, Wash, detected no HIV-1–positive individuals in this age group. Rates by racial/ethnic group and rates in 15- to 19-year olds could not be calculated because of the small number of specimens tested.

COMMENT

Rates of HIV-1 infection are alarmingly high in certain groups of adolescents and young adults. The most important determinants of HIV-1 risk are sexual and IV drug-using behaviors and geographic area. Seroprevalence rates were highest among IV drug users and male clients in STD clinics who had sex with other males. Seroprevalence rates among 20- to 24-year-old IV drug users attending STD clinics (range, 0% to 45.5%) and drug treatment centers (range, 0% to 33.3%) were similar. In both clinic settings, rates were highest in metropolitan areas that have high numbers of AIDS cases associated with IV drug use.[17] The fact that young IV drug users were being seen for STDs indicates they may have engaged in unprotected intercourse and, if infected with HIV-1, may have potentially infected their sex partners.

In STD clinics, young men aged 20 to 24 years who had sex with other males had very high seroprevalence rates across the United States, ranging from 9.7% to 55.6%. As a group, homosexual and bisexual males have changed their behaviors substantially as a response to HIV-1.[18] However, these high rates in young homosexually active men, who are likely to have been recently infected, indicate many are not practicing safe sexual behaviors. A study of West Coast homosexual men aged 18 to 25 years reported that 43% had engaged in unprotected anal intercourse during the previous 6 months.[19] The authors reported that young homosexual men thought AIDS only affected older homosexual men and may have believed that having unprotected intercourse with other young homosexual men is safe.

The percentage of adolescents in STD clinics identified as homosexual or bisexual in our survey was very small. Overall, only 1% of 15- to 19-year-old male clients in STD clinics were reported to have had sex with other males, compared with 5% of clients aged 20 years and older. Homosexually active male adolescents may be misclassified as heterosexual in our survey for several reasons. Male adolescents who have sex with other males often do not identify themselves as homosexual or bisexual, and may tell their clinicians they are heterosexual. Also, clinicians may feel uncomfortable asking male adolescents about homosexual practices, or clinicians who do ask questions related to sexual orientation may not record the information in the client's record. Improved collection of risk information and more detailed risk behavior studies are necessary to more accurately determine seroprevalence rates among male adolescents who have sex with males.

Among 15- to 24-year-old heterosexual clients in STD clinics with no reported risk for HIV-1, seroprevalence rates varied widely according to geographic location of the clinic. Metropolitan areas with the highest seroprevalence rates among heterosexuals were the same areas that had high numbers of AIDS cases among heterosexual IV drug users[17] and high seroprevalence rates among IV drug users attending drug treatment centers (ie, the Northeast, South, and Puerto Rico). Intravenous drug use most likely played a prominent role in transmission of HIV-1 in this heterosexual population. Some adolescents may be mistakenly identified as heterosexual with no reported risk because they are unaware of their sex partner's drug use or sexual histories, and some may be unacknowledged IV drug users themselves.

Among clients aged 20 years and older attending the same STD clinics, the median rates in heterosexual males were higher than in females in all age groups.[20] Among heterosexual adolescents, however, the reverse is true. Comparing median clinic rates by metropolitan area and sex, rates were significantly higher in 15- to 19-year-old females compared with males. This difference may be due to the greater efficiency of male-to-female sexual transmission of HIV-1, or young women may be having sex with older men who are more likely to be infected with HIV-1.

This relative prominence of HIV-1 in young females is seen in other settings as well. Among 17- to 19-year-old military recruits, seroprevalence rates in males (0.35 per 1000) and females (0.32 per 1000) were similar.[21] In 16-, 17-, and 18-year-old Job Corps trainees, the seroprevalence rates were higher among females (2.5 per 1000, 2.6 per 1000, and 4.1 per 1000, respectively) than among males (1.2 per 1000, 2.1 per 1000, and 3.1 per 1000, respectively).[22] Data from clinic surveys provide seroprevalence information on a population different from that of the military or Job Corps. The military excludes homosexuals, current drug users, and persons who have not completed high school. The Job Corps accepts homosexuals and high school dropouts, but current drug users are excluded. Because HIV-1 screening is mandatory and persons engaging in high-risk behaviors are to some extent excluded, seroprevalence estimates among military recruits and Job Corps trainees generally reflect a lower-risk population than at the clinics.

Seroprevalence rates among clients in women's health clinics were generally lower than among females in drug treatment centers and STD clinics. Women who have used IV drugs or have STDs are at increased risk for HIV-1 infection. However, some of the clients attending family planning, prenatal, or abortion clinics may be at lower risk because they may not practice high-risk behaviors, such as IV drug use or unprotected sexual intercourse. However, because 62% of the women's health clinics have identified at least one 15- to 24-year-old woman who is HIV-1 positive, seroprevalence in this population will be important to monitor.

Of the 13- to 24-year-old individuals with AIDS reported to the CDC, blacks and Hispanics are clearly overrepresented, with blacks accounting for 33.8% of cases and Hispanics, 19.3%.[12] However, among heterosexuals in STD and women's health clinics, the association between minority race/ethnicity and HIV-1 infection is not as clear cut. In women's health clinics, rates in black clients were significantly higher than in white or Hispanic clients. However, in STD clinics, rates in blacks were significantly higher than in Hispanics, but not significantly higher than in whites. In both clinic settings a substantial number of clinics had the highest rates in whites. Adolescents and young adults who attend these clinics practice similar behaviors and are at risk of HIV-1 infection regardless of their race or ethnicity.

These seroprevalence surveys provide important information regarding patterns of HIV-1 infection among adolescents and young adults attending selected clinics; however, these data have some limitations. First, because the clinics were not selected as a probability sample, these data are not necessarily representative of all adolescents in a given metropolitan area. The adolescents attending STD clinics, drug treatment centers, and women's health clinics have engaged in sexual and/or drug use behaviors that put them at greater risk for HIV-1 infection. Also, public urban clinics that routinely draw blood from all clients may serve youth at particularly high risk. Second, blinded surveys rely on information that is routinely collected by the clinics and available in the medical record. The quality of risk behavior information obtained varies among clinics. A substantial percentage of clients who have engaged in risk behaviors are probably misclassified as heterosexuals with no reported risk. Third, the data are limited by the small number of specimens tested in the drug treatment centers and among certain STD client groups, such as IV drug users and homosexual and bisexual males. Finally, because age was collected in 15- to 19- year-old and 20- to 24-year-old age groups, it is not possible to analyze differences in seroprevalence between younger and older adolescents and young adults. In 1990, the CDC began conducting surveys in adolescent clinics, homeless and runaway youth shelters, and juvenile detention centers in which exact age is collected so that these comparisons can be made.

Many adolescents attend STD clinics, women's health clinics, and drug treatment centers. However, services provided by these clinics are primarily designed for adults and may not be optimal for reducing high-risk behaviors in adolescents. Therefore, it is important for clinics to develop programs, clinic hours, and risk interventions specifically targeted toward youth. It is vital that clinic staff obtain a thorough history of risk behaviors, including homosexual activities.

Innovative education programs to teach adolescents about sexually transmitted diseases, condom use and family planning, and improved access to reproductive health services are essential. Special programs should be developed to reach male adolescents who have sex with other males, whether or not they identify themselves as homosexual or bisexual. Outreach to teenagers and young adults who are using drugs and are not in drug treatment programs is also critical. The future of the HIV epidemic will be determined largely by how we educate, protect, and care for today's youth.

We acknowledge the human immunodeficiency virus serosurveillance personnel in the state and local health departments and the clinic personnel for their efforts in conducting the surveys. We also thank Van Munn, Carolyn Sanchez, W. Meade Morgan, PhD, Susie Danner, and Steve James for their assistance with statistical analyses, software development, and data management; and Tim Dondero, MD, MPH, Kathryn Rauch, and James Curran, MD, MPH, for their editorial comments and overall program management.

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The Pediatric Branch, National Cancer Institute in Bethesda, Maryland, has over two dozen active treatment protocols for a wide variety of pediatric malignancies including diseases such as acute leukemia, non-Hodgkin's lymphoma, Ewing's sarcoma, osteogenic sarcoma, rhabdomyosarcoma, neuroblastoma and brain tumors. The Pediatric Branch has a 26-bed inpatient unit and extensive outpatient services including "day hospital" facilities. Children with newly diagnosed or recurrent malignancies, may be eligible for treatments.

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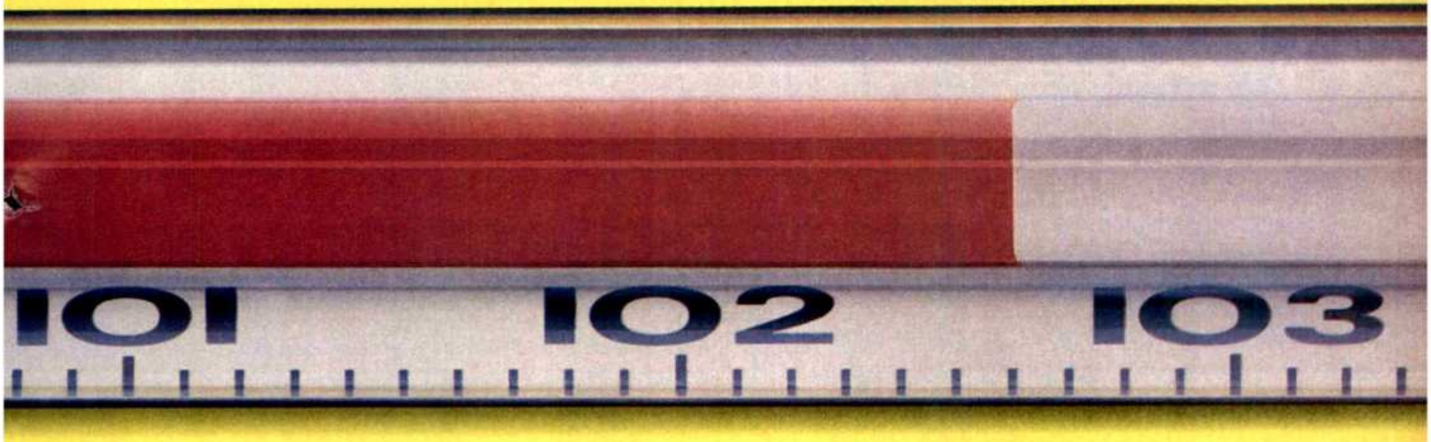

Superior reduction for fevers over 102.5°F

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For reducing children's temperatures over 102.5°F, ibuprofen 10 mg/kg was proven more effective than acetaminophen 10 mg/kg.[1]

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Please see brief summary of Prescribing Information on the next page.

References:
1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

A therapeutic alternative for fever

PediaProfen®

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **PediaProfen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **PediaProfen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Meaningful (3 times the upper limit of normal), elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with **PediaProfen**. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), **PediaProfen** should be discontinued.

Safety and efficacy of **PediaProfen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)	NDC 0045-0469-04
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SHAKE WELL BEFORE USING. Store at room temperature.

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While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Findings From the Preparticipation Athletic Examination and Athletic Injuries

obert H. DuRant, PhD; Robert A. Pendergrast, MD, MPH; Carolyn Seymore, MD; Gregory Gaillard; Josh Donner, MD

This study investigated the relationships between the findgs from a standardized preparticipation athletic examinan, the sport played, and athletic injuries requiring treatent by a physician and/or requiring the athlete to miss one more games. Of public high school students receiving a eparticipation athletic examination during the 1989-1990 ademic year, 674 (56%) either completed a telephone inrview or returned a mailed questionnaire at the end of the ademic year. The sample consisted of 408 (60.5%) blacks d 243 (36.1%) whites; 470 (69.7%) of the subjects were ales. The subjects ranged in age from 13 to 20 years ean±SD, 16.1±1.2 years), and participated in at least 10 hool sports. Injuries were reported by 29.5% of the athtes. The highest proportion of athletes injured occurred nong male football (36.3%), female basketball (33.3%), ale baseball (19.4%), male soccer (17.2%), and female ack and field (15.8%) participants. Responses by the athtes and their parents on the standardized health history ere significantly associated with injuries in several specific eas. Knee injuries were associated with previous knee inries, knee surgery, and history of injuries requiring medical eatment. Ankle injuries were associated with previous ane injuries and previous injuries requiring medical treatent. Both arm and other leg injuries were associated with evious fractures. Male athletes with either abnormal knee ankle findings from the physical examination were more ely to injure the knee or ankle, respectively. However, the nsitivities and positive predictive values of these relationips are weak. These data suggest that the preparticipation hletic examination may not predict certain athletic injuries d that additional prevention efforts for specific body areas injury are needed in certain sports.

(*AJDC.* 1992;146:85-91)

ports and other recreational activities are among the leading causes of nonfatal injuries among adolcents.[1-3] High school football players have consistently perienced higher injury rates than other athletes, but high injury rates also occur among track and field, baseball, basketball, gymnastics, wrestling, and field hockey participants.[1,4-6] Methodologic differences in study design make intersport comparisons of injury rates difficult. It has been difficult to accurately predict which athletes are at risk of injury from sports participation because of variations in the definition of athletic injuries, the training of the individual diagnosing and recording injuries, the methods of injury detection, how the injury rates are calculated, the time frames of the studies, and the populations studied.

Several investigators have proposed that the purpose of the preparticipation athletic examination (PAE) is to identify athletes who are at risk of injury, illness, or death from sports participation.[7-12] However, evidence that abnormal findings on the PAE predict an increased risk of athletic injury is inconsistent.[13-25] Most studies have reported that increased joint flexibility, ligamentous laxity, and previous injuries were associated with increased sprains, dislocations, and reinjuries.[15-25] Unfortunately, many of these studies were poorly designed and/or controlled, had low statistical power because of small sample sizes, or did not use appropriate statistical tests. In a well-controlled study, Lysens et al[26] conducted extensive physical examinations and psychological and behavioral tests on 185 college freshman physical education students in Belgium and monitored injuries for a period of 1 year. Although they found that several physical and psychological characteristics were associated with injuries, they pointed out that their sample was a self-selected population who were not likely to have experienced previous injuries that would have inhibited their participation in a highly demanding physical education program. Because their PAE protocol

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Purpose.—*This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.*

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Table 1.—Athletes Participating and Injured in Each Sport Stratified by Gender

Sport	No. (%) of Participants		No. (%) of Injuries		
	Males (N=470)	Females (N=204)	Males	Females	*P**
ootball	300 (63.8)	0	109 (36.3)	0	. . .
asketball	132 (28.1)	96 (47.1)	20 (15.2)	32 (33.3)	.0004
aseball/ softball†	108 (22.9)	99 (48.5)	21 (19.4)	9 (9.1)	.05
occer	58 (12.3)	0	10 (17.2)	0	. . .
ennis	20 (4.3)	26 (12.7)	2 (10.0)	2 (7.7)	NS
rack and field	103 (21.9)	57 (27.9)	11 (10.7)	9 (15.8)	NS
olf	26 (5.5)	4 (1.9)	2 (7.7)	0	NS
heerleading	0	15 (7.4)	0	1 (6.6)	. . .
ifle	1 (0.2)	0	0	0	. . .

*Kruskal-Wallis analysis of variance. NS indicates no statistical sig- icance.

†Baseball and softball are played by only males and females, spectively.

as far more comprehensive than is presently used in holastic athletic programs in the United States, the gen- al applicability of the findings is limited.

Although these studies suggest that a standardized PAE ight be able to detect adolescent athletes at increased risk sports-related injuries, no prior research has specifically ldressed this detail. In three previous studies, we have scribed and evaluated the PAE program in our public hool system.[7-10] The purposes of this study were to test hether findings from the PAE were predictive of athletic juries and to examine other factors associated with ath- tic injuries among high school students during the 1989-90 academic year.

SUBJECTS AND METHODS

PAE

The study protocol was approved by the Medical College of eorgia's Human Assurance Committee and the Athletic De- rtment of the Richmond County Board of Education. All 1204 iblic high school students in Richmond County, Georgia, who anned to participate in interscholastic sports during the 1989-90 academic year were required to undergo a physical exam- ation at the beginning of the sports season. Students could oose between an examination by a physician of their choice or station examination provided by volunteer physicians, den- ts, and physical therapists from the local community. How- er, all PAEs were recorded on the standardized Preparticipa- n History and Physical Examination Form previously commended by the American Academy of Pediatrics' Com- ittee on Practice and Ambulatory Medicine.[8,9,27] We did not cord who performed the examination on each athlete.

The station examination was performed in the outpatient partment of a community hospital. On scheduled evenings, oups of 50 to 100 students were evaluated. At the first ation, the health history was reviewed with the student; the ight, weight, pulse rate, and blood pressure were mea- red; and vision screening was completed. The students en circulated through seven other examination stations. The ntent of all components of the station examination has been eviously described.[8,28] Briefly, the following procedures ere used when examining each joint and muscle group.

Hamstrings.—The athlete was placed in a supine position on e examining table. The leg being tested was then flexed at the hip to 90° and held there by the athlete's hand. The leg was then extended slowly as far as possible without moving the thigh. If the leg could be extended completely, the hamstring was considered normal.

Spine.—First, the athlete was examined for scoliosis, kyphosis, or increased lumbar lordosis. Next, the athlete was placed in a sitting position with the knees flexed between 60° and 90°. The athlete was then asked to bend forward as far as possible, putting his or her head between the legs. Flexibility was then recorded as normal, tight, or very tight.

Knees.—Each knee was examined for alignment, effusion, active and passive range of motion, ligament integrity, and rotatory stability. A meniscus test was then done and specific joints were palpated.

Ankles.—Ankles were tested for heel cord tightness, range of motion, muscle strength in plantar flexion, dorsiflexion, inversion, eversion, and lateral and medial stability.

Shoulders.—The shoulders were examined for range of motion, joint stability, and muscle strength in flexion, extension, abduction, and internal rotation.

The history and physical examination results were then reviewed by one physician, and a recommendation was made concerning athletic participation. The students were either cleared for athletic participation without reservation, recommended not to participate after discussion with them and their coaches and/or parent(s), or cleared contingent on further evaluation, treatment, or conditioning. At the time of the examination, no examiner was aware of the purpose of the study.

Survey Design

The survey design used in this study has been previously described.[29] The standardized PAE form includes parental consent, biographical data, and home addresses and telephone numbers. In April 1990, letters were sent to the parents of all athletes explaining the purpose of the study. Using the telephone numbers provided by the students on the PAE forms, we attempted to contact by telephone all students who participated in interscholastic athletics during the academic year. All telephone contacts were made between 5 and 9 PM and were conducted during April and May 1990. Only 242 adolescents were at home during the period that the telephone calls were made. No parents or adolescents refused to be interviewed. In May 1990, all adolescents (n=962) not interviewed by telephone were mailed an identical questionnaire with a stamped, self-addressed return envelope. Four hundred thirty-two adolescents returned the questionnaire, resulting in 674 (56%) completing either the mailed questionnaire or the telephone interview. There were no differences between the interviews conducted by telephone and the mailed questionnaires in any variables measured.

Subjects

The subjects ranged in age from 13 to 20 years (mean±SD, 16.1±1.2 years). The sample consisted of 470 (69.7%) males, 408 (60.5%) blacks, and 243 (36.1%) whites, and was slightly skewed toward the 9th grade (36.6%), with fewer 12th graders (14.5%). The demographic data of the sample of 674 did not differ from those of the 530 adolescents receiving PAEs who were not interviewed.

Questionnaire

The questionnaire was designed to measure athletic injuries and attrition from scholastic sports.[29] The questionnaire was first pretested on a small group of male and female adolescents, and revisions were made in the wording of ambiguous items. The questionnaire obtained information about demographic variables, the sport for which the initial PAE was conducted (Table 1), attrition from any sport, and the reasons for attrition, and whether an injury was sustained during participation in school-sponsored sports that either required them to seek medical care from a physician and/or caused them to miss one or more games.

Table 2.—Injuries Occurring Among Athletes Participating in Male- and Female-Specific Sports

	No. of Athletic Injuries					
	Males			Females		
	Mean ± SD	Mean Rank	P*	Mean ± SD	Mean Rank	P*
Football						
Yes	0.50 ± 0.68	251.82	.0001			
No	0.24 ± 0.75	197.20		......	...	...
Basketball						
Yes	0.32 ± 0.84	210.47	.0083	0.44 ± 0.76	111.28	.002
No	0.44 ± 0.66	246.40		0.16 ± 0.44	92.64	
Baseball/softball						
Yes	0.55 ± 0.75	256.93	.008	0.34 ± 0.64	105.29	.021
No	0.36 ± 0.71	224.69		0.25 ± 0.62	97.93	

*Kruskal-Wallis analysis of variance.

Table 3.—Self-reported Athletic Injuries to Specific Areas of the Body

Location	No. (%) of Injuries*
Head	12 (1.8)
Neck	7 (1.0)
Back	13 (1.9)
Knee	61 (9.1)
Ankle	54 (8.0)
Foot	7 (1.0)
Leg, other than above	27 (4.0)
Shoulder	22 (3.3)
Elbow	5 (0.7)
Wrist	11 (1.6)
Arm, other than above	26 (3.9)
Kidney*	3 (0.4)
Ribs†	2 (0.3)
Heart†	3 (0.4)
Total	**253**

*Percentages based on 674 athletes.
†Represents those who responded to mailed questionnaires.

his definition of injury is more conservative than has been sed in either population-based studies[5] or prospective stud- s,[4,6,25,26] and was chosen because adolescents are not likely accurately recall injuries that are not significant enough to quire medical care or missing a game.[30] Athletes recorded e number of injuries sustained, the sport in which the jury(or injuries) occurred, and the part or area of the body jured. Because of a lack of knowledge of anatomy or ath- tic injuries, the adolescents were not asked to provide the edical diagnosis of their injury.

Statistical Analysis

For the purpose of this study, the outcome variables were as llows: experiencing an athletic injury, area of the body injured, d the total number of injuries sustained by each athlete. As- ciations among categorical variables were analyzed with χ^2 sts and the strengths of the associations were determined with coefficients. Significant relationships between findings from e health history or physical examination and athletic injuries ere then assessed for sensitivity, specificity, and positive and egative predictive value. Because of deviations from normality the distribution of the number of athletic injuries experienced y each athlete, this variable was analyzed with Kruskal-Wallis alysis of variance.

RESULTS

Among male athletes, a greater proportion of football players (36.3%) were injured than other athletes, followed in order by basketball, baseball, and soccer players (Table 1). The percentage of female basketball players (33.3%) experiencing athletic injuries was approximately the same as that of male football players (36.3%). A higher percentage of female than male athletes were injured participating in basketball ($P \leq .0004$) and track and field ($P > .05$), and a higher percentage of male baseball players than female softball players ($P \leq .05$) were injured (Table 1). No significant ethnic or age differences were found in injury rates within each sport. Injury rates did not vary by school. None of the schools employed certified trainers, and information was not collected on variations among coaches in training techniques.

Male adolescents experienced a significantly greater mean number of injuries (mean±SD, 0.41±0.72) than females (mean±SD, 0.29±0.63) ($P \leq .011$). The mean number of injuries sustained by football and baseball players was significantly greater than for other male athletes (Table 2). In contrast, male basketball players experienced a significantly lower mean number of injuries than other male athletes. Among female athletes, basketball and softball players sustained a greater mean number of injuries than other female athletes (Table 2).

The knee was the most frequently injured body part, followed in order by injuries to the ankle, leg, arm, and shoulder (Table 3). When injuries to specific areas of the body were examined within each sport and by gender, an increased risk of injury to the knee occurred among male football players (11.7% vs 7.0%) (Table 4). Female basketball players and male baseball players were at higher risk of ankle injuries. Male baseball players were also more likely to experience leg and arm injuries. Shoulder injuries were more likely to occur among male football, basketball, and soccer players, and head injuries occurred more frequently among male baseball players. Among the 57 female track and field participants, 15.8% experienced a knee injury, compared with 6.8% of other female athletes ($P \leq .048$).

More of the items on the standardized health history were significantly associated with athletic injuries than findings from the physical examination. Athletes experiencing dizziness, fainting, frequent headaches, or convulsions were slightly more likely to report a head injury during sports participation (Table 5). Having previously

Table 4.—Associations Between Athletic Injuries to Specific Areas of the Body and Sport Played by the Athlete (N=674)

	Football		Basketball		Baseball		Soccer	
	Yes (n=300)	No (n=374)	Yes (n=228)	No (n=446)	Yes (n=108)	No (n=566)	Yes (n=58)	No (n=616)
nee injury								
No. (%)	35 (11.7)	26 (7.0)	19 (8.3)	42 (9.4)	12 (11.1)	49 (8.7)	4 (6.9)	57 (9.3)
P	.034		NS		NS		NS	
*P**	.006		NS		NS		NS	
houlder injury								
No. (%)	18 (6.0)	4 (1.1)	2 (0.9)	20 (4.5)	2 (1.9)	20 (3.5)	6 (10.3)	16 (2.6)
P	.0008		.024		NS		.002	
*P**	.009		.011†		NS		.007	
nkle injury								
No. (%)	27 (9.0)	27 (7.2)	25 (11.0)	29 (6.5)	18 (16.7)	36 (6.4)	3 (5.2)	51 (8.3)
P	NS		.044‡		.0003		NS	
*P**	NS		NS		.0002§		NS	
lead								
No. (%)	6 (2.0)	6 (1.6)	3 (1.3)	9 (2.0)	7 (6.5)	5 (0.9)	0 (0)	12 (1.9)
P	NS		NS		.0003		NS	
*P**	NS		NS		.012§		NS	
eg								
No. (%)	16 (5.3)	11 (2.9)	12 (5.3)	15 (3.4)	9 (8.3)	18 (3.2)	4 (6.9)	23 (3.7)
P	NS		NS		.012		NS	
*P**	NS		NS		.035§		NS	
rm								
No. (%)	11 (3.7)	15 (4.0)	9 (3.9)	17 (3.8)	8 (7.4)	18 (3.2)	5 (8.6)	21 (3.4)
P	NS		NS		.0366		.049	
*P**	NS		NS		NS		NS	

Controlling for males. NS indicates no statistical significance.
$P>.05$ for females.
$P=.017$ for females only.
$P>.05$ for female softball.

erienced a knee injury or having undergone knee rgery was significantly associated with knee injuries ring the subsequent sports season. Similarly, previous kle injuries and previous injury requiring treatment by hysician were associated with ankle injuries during orts participation. Athletes who had previously broken one were more likely to injure a leg or arm during the orts season. Shoulder injuries were significantly ociated with other serious joint injuries in the past. wever, based on φ coefficients, the strength of each of se statistically significant relationships was weak ble 5). When the sensitivities and positive predictive ues of these relationships were analyzed, the informa- n contained in the health history was insufficient for physician to predict those athletes who would be ured (Table 6). Athletes who had previously broken a ne or had experienced other injuries requiring treat- nt by a physician had a significantly greater mean mber of injuries than other athletes (Table 7).

dolescents with either abnormal knee or ankle find- s during the physical examination were more likely to erience an athletic injury to the knee or ankle, respec- ely (Table 8). However, when gender was controlled, se relationships were only significant for male athletes the relationships were weak. The sensitivities were o low for these relationships. The positive predictive ue of the ankle component of the PAE was higher than that of the knee examination. This was partly due to there being only four males found to have abnormal ankles, three of whom were later injured. In comparison, 15 males were diagnosed as having abnormal knees, five of whom were later injured. No other variable had an effect on the relationships between findings on the PAE and athletic injuries.

COMMENT

The identification of risk factors for athletic injuries among adolescents has been difficult, partly due to the lack of a uniform definition of reportable injuries.[31] Some investigators have classified injuries by severity while others categorize injuries by class or time lost from participation.[6,17] For example, Prager et al[6] defined injury as an event causing an inability of the player to return to practice or the field of play for 48 hours. McLain and Reynolds[4] and Lanese et al[32] defined injury as any traumatic medical problem due to sports participation that results in a loss of time from practice or competition. However, they compute the number of days lost using different methods. Injury was defined by Lysens et al[26] as any event causing at least a 3-day absence from sports. When applied to the same group of athletes, these definitions will result in different injury rates. Consequently, comparisons of sport-specific injury rates among different studies are problematic. We chose a conservative definition of ath-

Table 5.—Associations Between Positive Finding From the Health History and Self-reported Injuries to Areas of the Body

Location of Injury During the Sports Season	Item/Area	Findings From the Health History			
		Yes, No. (%)	No, No. (%)	P	φ Coefficient
Head	Concussion				
Yes		1 (6.3)	11 (1.7)	NS	.05
No		15 (93.8)	636 (98.3)		
Head	Dizziness, fainting, frequent headaches, or convulsions				
Yes		2 (13.2)	10 (1.5)	.02	.13
No		13 (86.7)	638 (98.5)		
Neck	Neck injury				
Yes		0 (0)	7 (1.1)	NS	.01
No		1 (100.0)	648 (98.9)		
Knee	Knee injury				
Yes		15 (30.6)	44 (7.2)	.0001	.22
No		34 (69.4)	570 (92.8)		
Knee	Knee surgery				
Yes		3 (37.5)	56 (8.6)	.026	.11
No		5 (62.9)	598 (91.4)		
Ankle	Ankle injury				
Yes		8 (16.7)	45 (7.3)	.022	.09
No		40 (83.3)	569 (92.7)		
Ankle	Injuries requiring treatment by a physician				
Yes		11 (15.7)	42 (7.1)	.012	.10
No		59 (84.3)	550 (92.9)		
Leg, other	Broken bones				
Yes		9 (7.2)	16 (3.0)	.026	.09
No		116 (92.8)	521 (97.0)		
Shoulder	Other serious joint injuries				
Yes		2 (20.0)	20 (3.1)	.003	.12
No		8 (80.0)	632 (96.9)		
Arm	Broken bones				
Yes		9 (7.2)	15 (2.8)	.017	.09
No		116 (92.8)	522 (97.2)		

Table 6.—Sensitivity, Specificity, and Positive and Negative Predictive Values for the Associations Between Findings From the Health History and Athletic Injury

				Predictive Value, %	
History	Injury	Sensitivity, %	Specificity, %	Positive	Negative
Concussion	Head	8.3	97.7	6.3	98.3
Dizziness, fainting	Head	16.7	98.0	13.3	98.5
Neck injury	Neck	0.0	99.8	0.0	98.9
Knee injury	Knee	25.4	94.4	30.6	92.8
Ankle injury	Ankle	15.1	93.4	16.7	92.7
Knee surgery	Knee	5.1	99.2	37.5	91.4
Injury requiring treatment by a physician	Ankle	20.8	90.3	15.7	92.9
Broken bone	Leg or arm	36.7	82.5	14.4	94.2
Joint injury	Shoulder	9.1	98.8	20.0	96.9

ic injury to maximize the internal validity of the study. cause we were relying on adolescents' self report, we ere only interested in the injuries that were traumatic ough to require the athlete to seek medical care from a ysician and/or caused the athlete to miss one or more mes. We assumed that adolescents would be likely to curately recall injuries of this degree of severity.

In agreement with previous studies,[1,4-6] we found that otball players were more likely to be injured (36.3%) than athletes in any other sports, but the proportion injured was lower than has been previously reported. McLain and Reynolds[4] reported that 61% of the 179 football players in a Maywood, Ill, high school were injured during a single sports season. In an investigation of football injuries from 1982 to 1985, Prager et al[6] found that the proportions of athletes injured were 45.3%, 60.7%, 35.9%, and 27.0%, respectively. Powell[33] estimated that among the 1 million athletes participating in interscholastic foot-all, 28% had mild injuries, 5.9% had moderate injuries, nd 3.3% had major injuries. Football injury rates in other tudies vary considerably based on the definition of njury.[15-17] Our more conservative definition of injury may ccount for these differences. It also may be that our larger ample of football players (within one sports season) from greater number of high schools provides a more accuate estimate of football injuries.

When compared with data reported in a study by AcLain and Reynolds,[4] our athletes also had a lower rate f injuries in boys' basketball (37% vs 15.2%), girls' softall (13% vs 9.1%), and girls' track (18% vs 15.8%). Howver, we found slightly higher injury proportions in girls' asketball (33.3% vs 31%), boys' baseball (19.4% vs 15%), oys' soccer (17.2% vs 13%), boys' and girls' tennis (10.0% s 0% and 7.7% vs 3%, respectively), and boys' golf (7.7% s 0.0%). As was reported earlier for football injuries, inry rates reported in other studies vary substantially by njury definition, making comparisons difficult.[4,15,34,35]

Nicholas[14] and Godshall[13] have reported contradictory ata as to whether abnormal orthopedic findings on the reparticipation examination are predictive of athletic inry in high school students. Neither study, however, vas well controlled and neither study included appropri te statistical analysis of the data. Lysens et al[25] reported that muscle tightness found during the preparticipation examination was not associated with muscle strains. However, increased joint flexibility and ligamentous laxity were associated with increased sprains and dislocations. The finding by Lysens et al[25] confirms previous observations by Ekstrand and Gillquist,[18] Grana and Moretz,[20] and Kirby et al.[21] Lysens et al[25] also reported that abnormalities in feet configuration found during the preparticipation examination were associated with shin splints, chondromalacia patellae, Achilles tendon problems, and plantar fascitis during athletic competition. In contrast, we found that only two items on the physical examination component of the PAE were associated with athletic injuries and that the association applied only to male athletes. Male athletes with either abnormal knee or ankle findings on the PAE were more likely to injure the knee or ankle, respectively. However, these associations were weak, and the sensitivity and positive predictive values were low, indicating that the utility of the physical examination to predict these injuries was limited.

We found that more of the items on the health history portion of the PAE were predictive of athletic injuries than were findings from the physical examination. Considering that the most frequently injured body areas were the knee, ankle, leg, arm, and shoulder, the fact that each of these injuries was associated with findings on the health history is helpful. Specifically, previous injuries or having undergone surgery on a particular body area were associated with injuries during the subsequent sports season. However, as was found with the physical examination portion of the PAE, the associations between findings from the health history and actual injuries were weak and the sensitivities and positive predictive values were low. Previous studies also support the finding that athletes who report previous injuries are at higher risk of reinjury during athletic competition.[13-17,22-25] Data from the US Military Academy, West Point, NY, suggest that the majority of leg and knee injuries are reinjuries.[24] Lysens et al[25] reported that sprain, dislocation, and stress injuries showed the highest probability of recurrence.

From an epidemiologic viewpoint, the PAE can be

Table 7.—Injuries Associated With Findings From the Health History

	No. of Athletic Injuries		
	Mean±SD	Mean Rank	*P**
Finding from the health history	. . . . . .	. . .	. . .
Injuries requiring treatment by a physician			
Yes	0.58±1.12	365.44	.025
No	0.34±0.62	322.53	
Broken bones			
Yes	0.54±0.93	368.75	.0006
No	0.32±0.62	317.31	

*Kruskal-Wallis analysis of variance.

Table 8.—Associations Between Findings From the Physical Examination and Athletic Injuries

	Physical Examination Findings						Predictive Value, %	
	Normal, No. (%)	Abnormal, No. (%)	*P*	φ	Sensitivity, %	Specificity, %	Positive	Negative
Knee injury								
Yes	56 (8.6)	5 (29.4)						
No	596 (91.4)	12 (70.6)						
Total	**652**	**17**	.0032	.12	8.2	98.0	29.4	91.4
Males only knee injury								
Yes	38 (8.4)	4 (26.7)						
No	414 (91.6)	11 (73.3)						
Total	**452**	**15**	.049	.11	9.5	97.4	27.7	91.6
Ankle injury								
Yes	50 (7.5)	4 (66.7)						
No	613 (92.5)	2 (33.3)						
Total	**663**	**6**	.001	.20	7.4	99.7	66.7	92.5
Males only ankle injury								
Yes	36 (7.8)	3 (75.0)						
No	427 (92.2)	1 (25.0)						
Total	**463**	**4**	.001	.22	7.7	99.8	75.0	92.2

wed as a screening test for previously undetected risk njury or disease. As such, it fulfills the widely accepted teria for a screening test for large populations: specifily, it is relatively inexpensive, rapid, and noninvasive.[36] ur data indicate that the validity of the PAE in predicting k of injury may be fairly low. As the data for this study re collected in a well-organized station examination t has been established and refined for more than 10 rs,[7-10] it seems unlikely that further refinement of our eening tool will significantly improve the sensitivity or sitive predictive value for injuries. If so, the majority of uries in high school athletes will continue to occur in ing men and women who have demonstrated no abrmalities during the history or physical examination rtion of the PAE. This necessarily moves the focus of iny prevention in high school athletics away from the inidual athlete and to the environmental and social facs contributing to injury risk. Factors such as the pairing thletes for size and strength, selection of proper safety uipment, rules for fair play, and adequate preseason nditioning need to be addressed.

espite the need to broaden the scope of interest for ury prevention beyond the individual athlete, one not ignore the significance of a positive finding on the E. For example, our data suggest that almost 31% of ng athletes who report a history of knee injury will in subsequent athletic season sustain another knee ury significant enough to cause inability to participate t least one game or a visit to a physician. We can only culate as to how many of those reinjuries could have n prevented by intensive physical therapy and athletic ining, but we expect it would be a sizable proportion. ile we recognize that the majority of athletic injuries only be addressed by broader environmental conns, those athletes who demonstrate an abnormality on PAE form a high-risk group whose need for prevene therapy must not be ignored.

n summary, our data suggest that the PAE is a useful eening tool in identifying a small group of athletes at h risk of athletic injury. However, it also has demonated the importance of looking beyond the level of the lividual athlete into the broader environment in which letic events occur to address the greater scope of athc injuries.

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Severe Insulin Resistance and Diabetes Mellitus in Mandibuloacral Dysplasia

Gary R. Freidenberg, MD; David L. Cutler, MD; Marilyn C. Jones, MD; Bryan Hall, MD; Richard J. Mier, MD;
Floyd Culler, MD; Kenneth L. Jones, MD; Carmen Lozzio, MD; Silvia Kaufmann, MD

Mandibuloacral dysplasia (MAD) is a syndrome with on- in midchildhood. The predominant characteristics of AD include flexion contractures; mandibular hypoplasia; s of body fat; atrophic, speckled skin; and progressive teolysis of the clavicles. We studied three males with AD. Each had lipodystrophy of the extremities, with spar- of the face and neck. All had moderate hyperlipidemia. response to oral glucose, each had a diabetic response, th peak insulin levels between 2870 and 22 960 pmol/L. ulin-stimulated glucose disposal was determined in two tients with MAD. At an insulin infusion rate of 120 mU/m^2 r minute, glucose disposal was less than 25% of that asured at similar levels of insulinemia in nondiabetic ntrol subjects, indicating marked insulin resistance in pa- nts with MAD. The insulin resistance occurred without esity, excessive levels of counterregulatory hormones, or ti–insulin-receptor antibodies. We suggest that MAD is a eviously undescribed form of lipodystrophic insulin- istant diabetes mellitus.

(*AJDC.* 1992;146:93-99)

andibuloacral dysplasia (MAD) is a disorder commonly characterized by multiple joint contrac- res; atrophic, speckled skin; progressive osteolysis of clavicles and distal phalanges; and dental crowding sociated with mandibular hypoplasia. Short stature, pecia, hepatomegaly, and loss of body fat have also en reported. To date, a total of 20 subjects, from 10 nilies, have been described.[1-10] Inheritance of the MAD enotype has been reported to be autosomal recessive,[3] hough, with only 20 cases previously reported, this has t been established incontrovertibly.

We recently studied three patients with MAD. Each had partial lipodystrophy sparing the neck and face. Because of the known association of insulin resistance with other forms of lipodystrophy,[11-15] we sought to determine whether insulin resistance and diabetes mellitus developed in MAD.

PATIENTS, MATERIALS, AND METHODS

Patient Reports

PATIENT 1.—The fourth child of unrelated Hispanic parents, patient 1 had a birth weight of 3.5 kg. Abdominal distension, fullness of the neck, and contractures of the fifth fingers were first noticed at age 5 years. When examined for the first time at age 9½ years, his height was 140.5 cm (75th percentile for age), and his weight was 42.1 kg (95th percentile for age). Results of intelligence tests were normal. He had dark, curly scalp hair, a prominent dorsal cervical fat pad, conspicuous jowls, submental fullness, micrognathia, and a protuberant abdomen with mild hepatomegaly. His digits were narrow, and significant contractures of the interphalangeal joints of the hands and feet were present, with milder involvement of the wrists, elbows, ankles, knees, and hips. The skin had a speckled appearance; mild acanthosis nigricans of the nuchal area was confirmed with biopsy. Genital and pubic hair development were both classified as Tanner I. Results of audiometry indicated moderate bilateral hearing loss. Laboratory test values revealed abnormalities of liver function and hyperlipidemia. His serum aspartate aminotransferase value was 166 U/L (normal range, 10 to 45 U/L); alanine aminotransferase, 332 U/L (normal range, 10 to 45 U/L); alkaline phosphatase, 563 U/L (normal range, 30 to 130 U/L); cholesterol, 6.65 mmol/L (normal range, 3.10 to 4.40 mmol/L); triglycerides, 1.68 mmol/L (normal range, 0.34 to 1.58 mmol/L), and fasting plasma glucose, 5.0 mmol/L. Results of an open liver biopsy showed diffuse fatty infiltration.

By age 16 years, progressive loss of subcutaneous fat was noted in the extremities and in the trunk below the level of the nipples. This occurred despite consumption of greater than 27 300 kJ/d. Mild axillary acanthosis nigricans was observed. His genital and pubic hair development were classified as Tanner V. Laboratory values at this time were as follows: creatinine, 40 µmol/L; albumin, 47 g/L; total cholesterol, 4.55 mmol/L; high-density lipoprotein cholesterol, 0.85 mmol/L; and triglycerides, 4.84 mmol/L. His karyotype was 46,XY. His serum testosterone level was 11.0 nmol/L (normal range [Tanner V], 12.0 to 33.5 nmol/L), luteinizing hormone–releasing hormone, 11 IU/L (normal range for age, 3 to 10 IU/L); and follicle-stimulating hormone, 17 IU/L (normal range for age, 1 to 8 IU/L). Values for 24-hour urinary excretion of albumin and free cortisol were 711 mg and 170 nmol/d (normal range, 60 to 250 nmol/d), respectively; the creatinine clearance was 3.06 mL/s per 1.73 m^2 of body sur-

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rom the Departments of Pediatrics (Drs Freidenberg, M. Jones, Jones, and Kaufmann) and Medicine (Dr Cutler), University of lifornia, San Diego; the Department of Pediatrics, University of ntucky, Louisville (Drs Hall and Mier); the Department of Pedi- ics, University of Tennessee, Knoxville (Dr Lozzio); and the De- tment of Pediatrics, Emory University, Atlanta, Ga (Dr Culler).

resented in part at the Endocrine Society Meetings, Seattle, sh, June 21, 1989.

eprint requests to Indiana University, James Whitcomb Riley ildren's Hospital, A-593, 702 Barnhill Dr, Indianapolis, IN 46202 Freidenberg).

.ce area. Results of a percutaneous renal biopsy demon-rated focal tubular atrophy, interstitial fibrosis, and chronic iflammation with no evidence of immune complex deposi-on. A magnetic resonance image of the brain was normal. esults of a skeletal survey showed diffuse osteopenia and nall shoulder girdles, as indicated by short acromion pro-:sses that did not extend beyond the lateral edges of the wer ribs. As measured with dual roentgenogram absorpti-netry, fat-free mass (FFM) accounted for 86% of total body eight (TBW).

PATIENT 2.—The fifth child of unrelated parents, patient 2 was ie product of an uneventful, full-term gestation and weighed 4 kg at birth. He had small hands and arms and bilateral post-dial sixth toes; otherwise, he appeared normal. Contractures of ie metacarpophalangeal joints, interphalangeal joints, wrists, id shoulders were first noted at age 5 years and progressively orsened. Eventually, muscle atrophy was noted, with thinning : the skin, particularly over the joints. Bilateral sensorineural earing loss and myopia were detected at age 8 years. At age 17½ ears, his weight was 50 kg (≈3rd percentile for age), and his eight, 170 cm (≈25th percentile for age). He had a eunuchoid ibitus, with thin extremities and severe flexion deformities of ie elbows, hips, ankles, knees, and interphalangeal joints. He so had mild exophthalmos and micrognathia. His palate was gh, and maxillary hypoplasia was accompanied by dental ercrowding. Marked fullness of the neck was present. His avicles were easily palpated. The abdomen was protuberant, id the liver measured 15 cm at the midclavicular line. He had inner I genitalia and pubic hair. His arms and legs were thin id covered with speckled, parchmentlike skin. No visible :anthosis nigricans was noted. He had reduced muscle mass id little subcutaneous fat despite consuming to 18 900 to 21 000 /d. Results of routine laboratory tests were normal, except for ı alanine aminotransferase value of 80 U/L. His total cholesterol ılue was 5.55 mmol/L, very low–density lipoprotein choles-rol, 4.20 mmol/L; low-density lipoprotein cholesterol, 0.90 mol/L; high-density lipoprotein cholesterol, 0.45 mmol/L; and tal triglycerides, 13.0 mmol/L. His serum testosterone level as 1.0 nmol/L; follicle-stimulating hormone, 95 IU/L; and teinizing hormone, 96 IU/L. His karyotype was 46,XY. A 24-our urine collection contained 0.105 mg of protein. The creat-ine clearance was 3.08 mL/s. Results of a skeletal survey vealed radial and ulnar bowing, diffuse osteopenia, contrac-res of the fourth and fifth fingers, and a hypoplastic sacrum; ie joints and clavicles were normal. A magnetic resonance im-;e of the brain showed mild cortical atrophy.

PATIENT 3.—Patient 3, a 41-year-old man, was diagnosed to ive Werner syndrome at age 24 years.[10] His early development as normal; there was no parental consanguinity. At age 7 to 8 ears, he was noted to have a distended abdomen, dental over-owding, thin extremities, and loss of subcutaneous fat. His in was thin and taut, particularly over the hands, feet, and ırs. He had thick scalp hair, diffuse speckling of the skin, flex-n contractures of all the proximal interphalangeal joints, and small mandible. Pubertal development was classified as Tan-er I at age 14 years. Results of a testicular biopsy showed infan-e seminiferous tubules. With testosterone therapy, he had ormal adolescent growth and developed axillary and pubic ıir; eventually, a bilateral orchiectomy was performed for un-ıown reasons. He had marked sensorineural hearing loss. His ıryotype was 46,XY. At age 26 years, his blood urea nitrogen as 4.30 mmol/L; serum creatinine, 40 μmol/L (normal range, 40 110 μmol/L); serum triglyceride, 1.82 mmol/L; total choles-rol, 5.30 mmol/L; low-density lipoprotein cholesterol, 4.00 mol/L; high-density lipoprotein cholesterol, 0.90 mmol/L; and ery low–density lipoprotein cholesterol, 0.40 mmol/L. His fast-g serum glucose level was 6.4 mmol/L. At age 41 years, his eight was 81.8 kg, and his height, 180 cm. On the average, he ınsumed 14 700 kJ/d. Results of intelligence tests were normal. e had prominent eyes, with arcus senilis, a small chin, a pro-berant abdomen, and loss of body fat, sparing the neck and ce. His extremities were thin, and the skin was taut and speckled. He had contractures of the fingers, hips, and ankles. Mild acanthosis nigricans was visible in the nuchal and axillary areas.

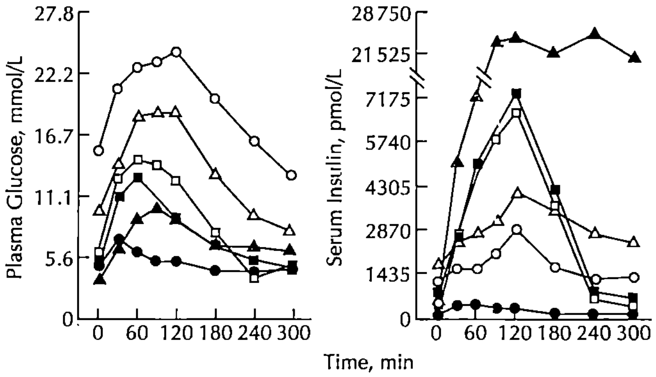


Fig 1.—*Results of oral glucose tolerance tests. Glucose and insulin levels were measured serially after a standard 1.75-g/m² (75-g maximum) oral glucose load. Data are means in five control subjects (solid circles), patient 1 at age 12 years (solid triangles), patient 1 at age 16 years (open triangles), patient 2 at age 17 years (open circles), patient 3 at age 24 years (solid squares), and patient 3 at age 41 years (open squares). To convert glucose to milligrams per deciliter divide by 0.0555; to convert insulin to microunits per milliliter, divide by 7.175.*

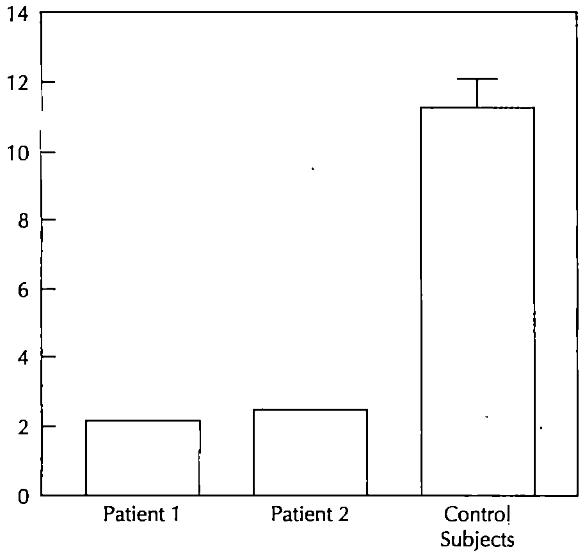
Materials and Methods

Glucose clamp studies and glucose tolerance tests were performed with informed consent in patients 1 and 2 and in five nondiabetic, nonobese men (ages 22 to 46 years) who served as control subjects. Studies and tests were performed at the Clinical Research Center, University of California San Diego Medical Center, according to protocol approved by the Human Subjects Review Committee. None of the subjects used any medications known to alter glucose metabolism. Glucose tolerance tests were conducted at the Clinical Research Center in San Diego for the relatives of patient 1, and at the Human Development Center at the University of Tennessee Medical Center, Knoxville, for the relatives of patient 2.

Glucose tolerance was evaluated in response to an oral glucose load (1.75 g/kg, with a maximum of 75 g) according to standard protocol and guidelines prescribed by the National Diabetes Data Group.[16] The response to exogenous insulin administration was assessed using the euglycemic clamp technique as previously described.[17] A primed continuous infusion of insulin was administered at 120 mU/m² per minute in addition to tritiated glucose (New England Nuclear, Boston, Mass). Plasma glucose measurements were performed at 5-minute intervals, and adjustments were made as necessary in the rate of infusion of a 20% dextrose solution to maintain a plasma glucose level of 5.5 mmol/L. The rate of glucose disposal (G_d) was calculated using the Steele equations in modified derivative form.[18,19] Glucose disposal was measured during the final 40 minutes of a 3-hour insulin infusion.

Hypothalamic-pituitary function was assessed before the study and after the simultaneous administration of three different hypothalamic-releasing hormones. Blood was drawn serially for testing of corticotropin, cortisol, growth hormone, and thyroid-stimulating hormone levels before and after the administration of a mixture of corticotropin-releasing hormone (1 μg/kg), growth hormone–releasing hormone (1 μg/kg), and thyrotropin-releasing hormone (200 μg/kg). Growth hormone secretion was also assessed in one patient using intravenous arginine hydrochloride (0.5 g/kg) and oral levodopa (500 mg).

Serum growth hormone,[20] insulin,[21] corticotropin,[22] thyroid-stimulating hormone,[23] glucagon,[24] and catecholamines[25] were measured using radioimmunoassay. The presence of anti–insulin-receptor antibodies was ascertained using described methods.[26]



g 2.—*Insulin-mediated glucose disposal. Glucose disposal was easured at euglycemia at the end of a primed continuous infusion f insulin at a steady-state rate of 120 mU/m² per minute. Results are own for patient 1, patient 2, and five control subjects, and are ven as means±SEMs. To convert glucose disposal to micromoles er kilograms of body weight per minute, multiply by 5.55.*

RESULTS

Oral Glucose Tolerance Tests

The results of oral glucose tolerance tests performed for l three patients are displayed in Fig 1. In patients 1 and glucose tolerance was measured twice, with a separaon of 4 and 17 years, respectively. When studied at ages 1 and 41 years, patient 3 had normal fasting glucose levels ut a diabetic response to oral glucose. Patient 1 had a noral fasting blood glucose level and normal glucose tolernce at age 12 years, but was diabetic by age 16 years. Paent 2 was clearly diabetic when studied at age 17 years.

Levels of serum insulin were elevated in the fasting ate and rose markedly in response to a glucose load in l three patients. Insulin levels in patient 3 remained reltively constant during a 17-year period. The magnitude f the hyperinsulinemia was more marked in patient 1 at ge 12 years, when he had normal glucose tolerance, ompared with age 16 years, when he was clearly diabetic.

In Vivo Glucose Disposal

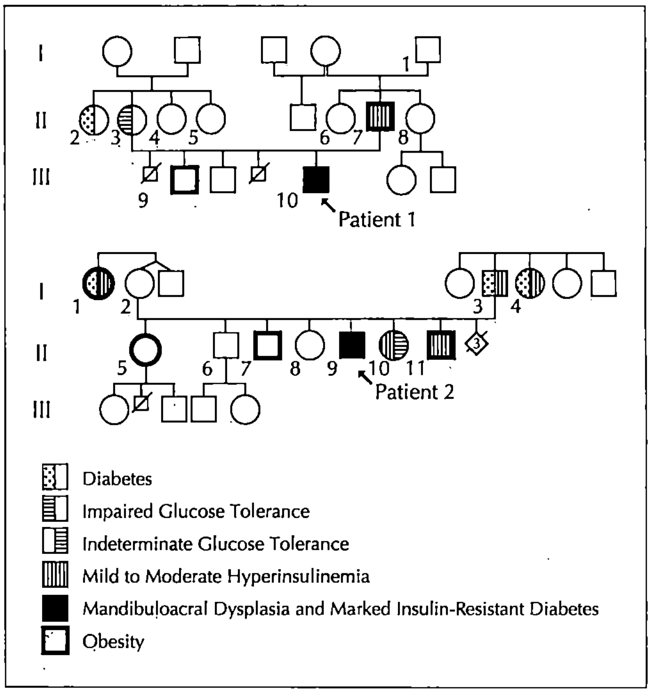
Marked hyperinsulinemic responses to oral glucose, egardless of normal or diabetic glucose tolerance, sugested insulin resistance in all three patients. To verify is, we assessed the ability of exogenous insulin to stimlate G_d in two of the three subjects. Measured during uglycemia at an insulin infusion rate of 120 mU/m² per inute, G_d was 2.13 mg/kg per minute in patient 1 and .45 mg/kg per minute in patient 2, compared with 1.3±0.8 mg/kg per minute in control subjects (Fig 2).

Circulating Insulin Antagonists

Levels of glucose counterregulatory hormones, meaured in two patients, did not appear to account for the sulin resistance. In a fasting state, the respective levels f counterregulatory hormones in patients one and two ere as follows: glucagon, 180 and 310 ng/L (normal range asting], 50 to 250 ng/L); norepinephrine, 1.15 and 1.40 mol/L (normal range [supine], 0.88 to 2.65 nmol/L); epiephrine, 170 and 130 pmol/L (normal range [supine], 0 to 820 pmol/L); growth hormone, 0.5 and 5.0 μg/L; and cortisol, 390 and 410 nmol/L (normal range, 160 to 660 nmol/L). The thyroxine and triiodothyronine values were 91 nmol/L (normal range, 58 to 155 nmol/L) and 2.6 nmol/L (normal range, 1.0 to 3.4 nmol/L), respectively, in patient 1 and 114 nmol/L and 2.7 nmol/L in patient 2.

Results of evaluation of the hypothalamic-pituitary axis were abnormal in both patients. Patient 1 had a negligible peak growth hormone level of 1.5 μg/L after administration of growth hormone–releasing hormone and a diminished response to arginine and L-dopa, with a peak level of growth hormone of 6.4 μg/L at age 10 years and a peak level of 0.9 μg/L at age 15 years; his somatomedin C level at age 15 years was 340 U/L (normal range, 900 to 3100 U/L). Patient 2 had hypergonadotropic hypogonadism.

Serum from the three patients was tested for the presence of anti–insulin-receptor antibodies. A 1:200 dilution of polyclonal antireceptor serum inhibited tracer insulin binding to IM-9 lymphocytes by 72%, whereas a 1:50 dilution of sera from the three patients and two control subjects inhibited tracer insulin binding to IM-9 by less than 4%.


I
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Patient 1
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Patient 2
Diabetes
Impaired Glucose Tolerance
Indeterminate Glucose Tolerance
Mild to Moderate Hyperinsulinemia
Mandibuloacral Dysplasia and Marked Insulin-Resistant Diabetes
Obesity

Fig 3.—*Pedigrees and results of metabolic studies. Oral glucose tolerance tests were performed in multiple family members of the pedigrees of patients 1 (top) and 2 (bottom). For detailed results of the metabolic studies, see Tables 1 and 2.*

Family Studies

The pedigrees of patients 1 and 2 and the results of metabolic studies of these patients and their family members are shown in Fig 3 and Tables 1 and 2 . In the family of patient 1 (Fig 3, top), several abnormalities of carbohydrate metabolism were detected: II-2 had fasting hyperglycemia and relative insulinopenia; II-3 had impaired glucose tolerance; and II-7 had hyperinsulinemia consistent with his degree of obesity. None of patient 1's extended family had an MAD phenotype. Various abnormalities of carbohydrate metabolism were also noted in patient 2's family (Fig 3, bottom). Uncontrolled type II diabetes mellitus was identified in I-1. In addition, I-3 had

Table 1.—Results of Metabolic Studies of Patient 1 and His Family*

Family Member	Age, y	BMI, kg/m²	Fasting Levels Glucose, mmol/L	Insulin, pmol/L	HbA$_{1c}$	Cholesterol, mmol/L	Triglyceride, mmol/L	AUC Glucose, mmol/L·min^{-1}	Insulin, pmol/L·min^{-1}
II-2	52	24.1	21.6	55	0.122	7.40†	2.02	NA	NA
II-3	45	25.4	6.2	110	0.061	7.80†	1.96	2082	113 650
II-4	47	25.0	5.3	70	NA	NA	NA	1995	98 045
II-5	49	23.9	5.4	60	NA	NA	NA	1882	54 135
II-7	46	40.1	5.9	240	0.050	4.50	2.08	1994	243 990
III-9	26	30.0	5.3	100	0.054	4.50	1.80	1753	113 865
III-10	10	21.3	4.0	480	NA	6.65†	1.68	2204	5 696 700
III-10	15	24.3	9.4	1710	0.068	4.55	9.84†	4108	748 320
Control subjects	NA	NA	4.4±.2	80±10	0.038-0.063	NA	NA	1502±248	86 820±15 250

'AUC indicates areas under curves; BMI, body mass index; HbA$_{1c}$, glycosylated hemoglobin A; and NA, not applicable or data not avail-e. Areas under curves for glucose and insulin plots were calculated from the values obtained 0, 30, 60, 90, 120, 180, 240, and 300 minutes er administration of oral glucose. Values for control subjects are given as means ± SEMs. To convert cholesterol and triglyceride levels milligrams per deciliter, divide by 0.02586 and 0.01129, respectively. For AUC, divide by 0.0555 to convert glucose to milligrams per de-ter per minute, and divide by 7.175 to convert insulin to microunits per milliliter per minute. Family members are shown in Fig 3, top.

·Values are more than 2 SDs higher than the mean for age.

Table 2.—Results of Metabolic Studies of Patient 2 and His Family*

Family Member	Age, y	BMI, kg/m²	Fasting Levels Glucose, mmol/L	Insulin, pmol/L	Cholesterol, mmol/L	Triglyceride, mmol/L	AUC Glucose, mmol/L·min^{-1}	Insulin, pmol/L·min^{-1}
I-1	42	28.5	18.0	905	5.80	9.82†	NA	NA
I-2	48	NA	4.6	70	6.20	2.30	1830	91 375
I-3	50	NA	5.4	90	5.20	1.74	2970	228 810
I-4	44	19.7	NA	NA	NA	NA	NA	NA
II-5	28	34.1	4.5	70	4.90	1.30	1580	137 115
II-6	27	NA	NA	NA	3.35	1.00	NA	NA
II-7	26	29.2	4.6	120	3.05	0.50	1660	113 435
II-8	19	18.4	5.6	115	2.90	0.86	2048	92 125
II-9	17	17.3	15.3	1205	4.90	3.74†	5862	506 915
II-10	16	20.8	5.2	40	3.85	1.58	1918	21 740
II-11	13	31.0	5.3	220	4.80	3.04†	2084	287 570
Control subjects	NA	NA	4.4±.2	80±10	NA	NA	1502±248	86 820±15 250

'Abbreviations, methods, and conversions to conventional units of measure are explained in the first footnote to Table 1. Family mem-rs are as shown in Fig 3, bottom. The glycosylated hemoglobin A value in patient 2 was 0.086.

·Values are more than 2 SDs higher than the mean for age.

sting euglycemia, but a diabetic response to an oral glu-se load. Results of a glucose tolerance test in II-10, who d mild hyperinsulinemia, were indeterminate.[16] Eu-/cemia and hyperinsulinemia, consistent with moder-: obesity, were identified in II-11. Family member I-4 d a history of type II diabetes mellitus. The MAD phe-ıtype was not observed in any family members.

COMMENT

We describe three unrelated males with MAD and di-etes mellitus; none was ketonuric. One previously re-ırted[5] adolescent female with MAD also had diabetes. l of our subjects had marked hyperinsulinemia in a sting state after administration of oral glucose; in addi-ın, of the two patients tested, both had substantially re-ıced responses to administration of exogenous insulin. together, these findings indicate severe insulin resis-ıce as the cause of the diabetes in MAD.

The cause of the insulin resistance in MAD is unknown. Our investigations showed that it was unrelated to obesity, excessive counterregulatory hormones, or antibodies to insulin receptors. Given the resistance to exogenous insulin, it was unlikely that the diabetes associated with MAD was due to an inactive mutant insulin.[27] Furthermore, acanthosis nigricans was either absent or not prominent, suggesting that the insulin resistance was unrelated to that described in type A insulin-resistant diabetes.[28]

Several family members of patients 1 and 2 had abnormalities of glucose metabolism, which raises the question of whether some dominantly transmitted form of diabetes, such as non–insulin-dependent diabetes mellitus (NIDDM) or maturity-onset diabetes of youth (MODY), was inherited coincidentally with the MAD phenotype.[29] However, for several reasons it was unlikely that NIDDM or MODY was the primary cause of diabetes in our

Table 3.—Characteristics of Lipodystrophy Syndromes*

	Complete Lipodystrophy		Partial Lipodystrophy		
	Congenital	Acquired	Cephalothoracic	Familial	MAD-Related
Predominant inheritance	AR	S	S	XLD	AR
Incidence, F:M	1:1	F>>M	4:1	F>>>M	1:2
Lipoatrophy	F, T, L	F, T, L	F, T	L or T, L	T, L
Hyperlipidemia	+	+	±	+	+†
Glucose intolerance	+	+	±	+	+†
Hyperinsulinemia	+	+	+	+†	+†
Hepatomegaly	+	+	–	±	+†
Nephritis	–	–	+	–	–
Genital hypertrophy	+	Rare	±	±‡	–
Hypogonadism	–	–	–	–	+†
Bone age	Advanced	Normal	Normal	Normal	Normal
Joint contractures	–	–	–	–	+
Mandible	Large	Normal	Normal	Normal or large§	Small

*MAD indicates mandibuloacral dysplasia; AR, autosomal recessive; S, sporadic; XLD, X-linked dominant, with suspected lethality in ales; >>, much greater than; F, face; T, trunk; L, limbs; plus sign, present; minus sign, absent; and plus or minus sign, sometimes resent.

†Frequency of occurrence is not well established.

‡Pseudohypertrophy is due to increased pubic fat.

§Normal in type I form of lipodystrophy and large in the type II form of lipodystrophy.

atients. First, although there is considerable heterogeeity of insulin secretory responses to oral glucose, peak sulin levels rarely exceed 2150 pmol/L in lean or obese bjects with untreated NIDDM or MODY.[29-31] Our paents had peak insulin levels of 21 525 pmol/L (patient 1), 370 pmol/L (patient 2), and 7175 pmol/L (patient 3).

Second, the degree of insulin resistance was more seere in our patients than in most patients with NIDDM or IODY. For example, at the insulin infusion rate of 120 U/m^2 per minute used for our clamp studies, patients 1 nd 2 had G_d rates of 2.13 mg/kg per minute and 2.45 g/kg per minute, respectively. These values are quite w compared with the mean G_d of 5.4±0.5 mg/kg per inute described in nonobese subjects with NIDDM who ceived insulin at the same infusion rate.[32] The low G_d tes in MAD are even more strikingly reduced, relative) values in NIDDM, when G_d is expressed in terms of t-free mass (FFM) rather than total body weight (TBW). ecause insulin-stimulated G_d is largely a function of uscle mass,[33] it is meaningful to express G_d in terms of FM, especially when comparing patients with NIDDM ith patients with lipodystrophic MAD who have obvius differences in fat mass. Fat-free mass accounted for 75% of TBW in patients with NIDDM described by umbiner et al[32] and for 86% of TBW in patient 1. Recallated as a function of FFM, G_d would be ≈7.1±0.7 g/kg of FFM per minute in patients with NIDDM vs 2.48 g/kg of FFM per minute in patient 1. In the three reports f MODY in which insulin resistance was studied, G_d rate as ≈5 mg/kg of TBW per minute at insulin infusion rates f <120 mU/m^2 per minute.[34-36] Thus, G_d in patient 1 was 3 SDs below the mean G_d in patients with NIDDM or IODY, indicating that the degree of insulin resistance in ur patients was more severe than that seen in most, if not ll, patients with NIDDM or MODY.

Third, patients 1 and 2 appeared to be much more inlin resistant than their parents. When studied using lucose clamps, patient 1 was certainly more insulin resistant than his mother, who had impaired glucose tolerance, a condition characterized by milder insulin resistance than that seen in NIDDM, when studied using glucose clamps.[37] Patient 1's father was hyperinsulinemic, but his degree of hyperinsulinemia was sufficient to prevent diabetes; much higher levels of insulin in his diabetic son were insufficient, indicating greater insulin resistance in patient 1 than in his father. Similar arguments can be made for patient 2, whose mother had no evidence of insulin resistance or diabetes. Both patient 2 and his father were diabetic and hyperinsulinemic; yet, a fasting insulin level of 1205 pmol/L in patient 2 did not prevent fasting hyperglycemia, whereas an insulin level of 70 pmol/L was associated with a normal fasting blood glucose level in the father. Collectively, these results indicate greater insulin resistance in patients 1 and 2 compared with their parents.

Thus, the data strongly suggest that the insulin-resistant diabetes in all three patients with MAD was not merely the result of the coincidental inheritance of NIDDM or MODY. However, given the prevalence of diabetes in the pedigrees, we cannot exclude the possibility that the insulin resistance and diabetes seen in our patients resulted from the coinheritance of a dominantly inherited diabetic gene, such as a "gene" for NIDDM or MODY, from one parent, and an abnormal, but phenotypically silent, gene from the other parent, with the combination resulting in severe diabetes and an MAD phenotype. Alternatively, of course, diabetes and insulin resistance may be inherited with MAD as a single autosomal-recessive trait, in which case the glucose and insulin abnormalities in the unaffected family members of patients 1 and 2 would be coincidental. We cannot now determine which scenario accurately explains the causes of the insulin resistance seen in our patients. Further studies, including studies using glucose clamps, of the families of other patients with MAD will be necessary to establish a definite link between the MAD phenotype and insulin-resistant diabetes.

t is possible that the glucose, insulin, and lipid abnor- lities in patients with MAD are related to decreased cutaneous fat. Four types of lipodystrophy have been viously described and all have been associated with ying degrees of insulin-resistant diabetes and perlipidemia.[11-15,38] Despite these metabolic similarities, ique somatic features of MAD distinguish it from own forms of lipodystrophy (Table 3). Whether lipo- strophy occurs in all patients with MAD is un- own. Including the patients described in this report, cases of MAD have now been described. At least 13 these 22 involved some loss of body fat[1,2,5-10]; loss of dy fat in the other nine cases is uncertain owing to ufficient documentation. Based on these data, we culate that lipodystrophy may occur in most pa- nts with MAD.

Whether insulin resistance and/or diabetes invariably ur with lipodystrophy-associated MAD is unclear from scant published data. Insulin levels were unreported the 19 previous cases of MAD, and results of glucose dies were mentioned for only four patients.[1,5,8] Our ients had both lipodystrophy and insulin-resistant di- tes mellitus; in one, marked insulin resistance was sent at least 4 years before diabetes was diagnosed. is raises the possibility that insulin resistance has gone detected in other patients with MAD because insulin els were not measured and symptomatic diabetes may t have yet developed.[1-10]

f the two patients tested, minimal growth hormone retion and reduced somatomedin level were evident in (patient 1). The reason for his low level of growth rmone is not obvious. Possible explanations include a tral nervous system abnormality similar to that pro- sed in congenital lipodystrophy,[39] suppression by hy- glycemia,[40,41] or inhibition by heterologous binding of h levels of insulin to insulinlike growth factor–1 eptors in the pituitary gland and hypothalamus.[42,43] ding of insulin to insulinlike growth factor–1 receptors tside the brain could mediate growth and account for rmal adult stature in patient 1 despite his hyposoma- ropism.

ur studies suggest that, in addition to abnormalities lucose metabolism, hypogonadism may be part of the D phenotype. An elevated level of gonadotropins and repubertal testosterone concentration indicated pri- ry hypogonadism in one of our patients (patient 2); a ond patient (patient 3) had a history of hypogo- dism.[10] In addition, two previously described males h MAD who received testosterone for absent sexual turation may also have had hypogonadism.[3,4] Un- ated hypogonadism may contribute to the muscular ophy seen in one of our patients in contrast to the scular hypertrophy seen in our other two patients and patients with other forms of lipodystrophy.

Mandibuloacral dysplasia is a distinct clinical syndrome which subjects who are normal at birth develop typical natic features within the first decade of life. Associated dings may include diminished hearing, primary hy- gonadism, abnormalities of growth hormone release, d partial lipodystrophy. Our data suggest that severe ulin-resistant diabetes mellitus is also part of the MAD enotype. The cause of the insulin resistance in MAD is clear. Mandibuloacral dysplasia appears to be a previ- sly unrecognized form of partial lipodystrophy associ- d with insulin-resistant diabetes.

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Clinical Features of Vascular Thrombosis Following Varicella

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Objective.—To define the clinical characteristics, neuroimaging features, and outcome of five patients with post–primary varicella zoster virus infection hemiparesis and to offer a hypothesis to explain the predilection for the involvement of the cerebral vasculature in this condition.

***Design.*—Patient series.**

***Setting.*—Five patients were treated during a 14-month period in a private pediatric neurology practice in a medium-size southwestern city.**

***Interventions.*—Steroids (two patients) and antiplatelet drugs (two patients). No observed effects of therapy.**

***Results.*—The onset of the hemiparesis occurred several weeks (mean, 5.4 weeks) following an episode of the chickenpox. Magnetic resonance imaging was more sensitive than computed tomography or angiography in demonstrating the area of involvement deep in the cerebral hemispheres. The prognosis was good regardless of the therapy administered, as all patients recovered completely or nearly completely.**

***Conclusions.*—Primary varicella zoster virus infection with delayed-onset hemiparesis typically occurs approximately 6 weeks after primary varicella zoster virus infection. Magnetic resonance imaging is the most sensitive neuroimaging tool in these children. The prognosis is good, with recovery of function and no recurrences in our patients. The innervation of the carotid artery and the characteristics of the varicella zoster virus itself together provide the local and systemic factors that may trigger the vasculopathy responsible for this syndrome.**

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A variety of nervous system manifestations of primary varicella zoster virus (VZV) infections (chickenpox) have been reported. These include encephalitis, meningoencephalitis, aseptic meningitis, myelitis, postinflammatory leukoencephalopathy (acute cerebellar ataxia), Guillain-Barré syndrome, facial nerve palsy, and Reye's syndrome.[1] Neurologic complications of chronic VZV involving the trigeminal nerve (varicella zoster ophthalmicus) are also seen. Among the complications of chronic VZV infection is the occurrence of a delayed contralateral hemiparesis, presumably the result of direct viral spread to contiguous structures from the ophthalmic nerve, causing a cerebral angiopathy.[2] During the last decade, six patients with delayed-onset cerebrovascular thrombosis following primary VZV infections have been described in the English-language literature.[3-5] Although primary VZV infection is a systemic disease, evidence suggests that cerebral angiopathy also underlies the cerebrovascular event in these patients.[4] To our knowledge, no explanation of the predilection for involvement of the cerebral vasculature in these patients has been provided.

Herein, we describe five children with delayed onset of hemiplegia 3 to 8 weeks following primary VZV infection and define the clinical characteristics, course, and neuroimaging features. The propensity of the VZV to produce a retrograde infection of the peripheral nerve, the intense sensory stimulus provided by the chickenpox lesions, the dense sympathetic innervation of the carotid artery, and the systemic reaction to the primary VZV infection provide a combination of local and systemic factors that may account for the unusual clinical features of this condition.

PATIENTS AND CLINICAL DATA

All five patients were treated by one of us (M.R.H.) during the 14-month period between May 1989 and July 1990. The presence of the preexisting chickenpox was ascertained by history from the parents. In each child, the diagnosis had been established on clinical grounds alone. Only one patient (patient 4) was not seen during the acute stage of the illness (Table). The patient ages ranged from 3 to 7 years (mean, 5.4 years). Patient 1 had right-sided weakness, and the remaining patients had left-sided involvement. The neurologic deficit had a stuttering onset (neurologic deficit developing in a stepwise fashion during a 6- to 36-hour period) in three patients (patients 1, 3, and 4). Two patients (patients 3 and 5) had seizures at onset, although patient 3 had a preexisting seizure disorder.

Laboratory studies, including neuroimaging studies, were performed in all patients. Electroencephalography in three patients (patients 1, 2, and 5) revealed unilateral findings in patients 1 and 2. Computed tomographic scans were abnormal in two of four patients, although the area of ischemia was seen on magnetic resonance imaging (MRI) scans in all patients. Only patient 5 had identifiable cortical involvement; the remainder had predominant involvement of the deep structures of the ce-

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Delayed-Onset Postvaricella Hemiparesis Patient Data*

Variables	Patients				
	1	2	3	4	5
Clinical Features					
Age, y/Sex (mean age, 5.4 y)	6/F	6/M	5/M	7/M	3/F
Interval from varicella to onset (mean, 5.4 wk)	3 wk	2 mo	6 wk	6 wk	1 mo
Hemiparesis	R	L	L	L	L
Arm	+	+	+	+	+
Leg	+	+	+	+	+
Face	+	+	+	+	+
Neurologic deficit at onset, complete (C)/stuttering (S)	S	C	S	C	C
Headache at onset	+	−	−	−	−
Lethargy/somnolence	+	−	+	−	+
Seizures at onset	−	−	+	−	+
Laboratory features					
Unilateral electroencephalographic findings	+	+	ND	ND	−
Computed tomographic evidence of stroke	+	ND	−	+	−
Magnetic resonance imaging evidence of stroke					
Deep	+	+	+	+	−
Cortex	−	−	+	−	+
Angiography (vasculopathy)	+	−	−	ND	ND
Echocardiography	−	−	−	ND	−
Hematologic evaluation	−	−	−	ND	−
Lumbar puncture	−	ND	ND	ND	−
Results					
Therapy: prednisone (S), dipyridamole (D), or aspirin (A)	S	. . .	. . .	D	S, A
Interval to follow-up examination, wk	8	8	6	8	5
Nearly complete recovery	+	+	+	+	+

*Plus sign indicates present; minus sign, absent; and ND, not done.

rebral hemisphere, including the basal ganglia and internal capsule (Figure). Of the three patients who underwent arteriographic examination, in patient 1 only the study showed evidence of vasculopathy with beading and segmental narrowing of the middle cerebral artery. Hematologic evaluation in four patients included determinations of protein C level, protein S level, antithrombin III antibody level, platelet count, antinuclear antibody titer, rheumatoid factor level, and erythrocyte sedimentation rate, as well as lipoprotein electrophoresis. Results were normal in all patients. Echocardiography yielded normal findings in the four patients in whom this procedure was performed. Lumbar puncture yielded normal findings in patients 1 and 5.

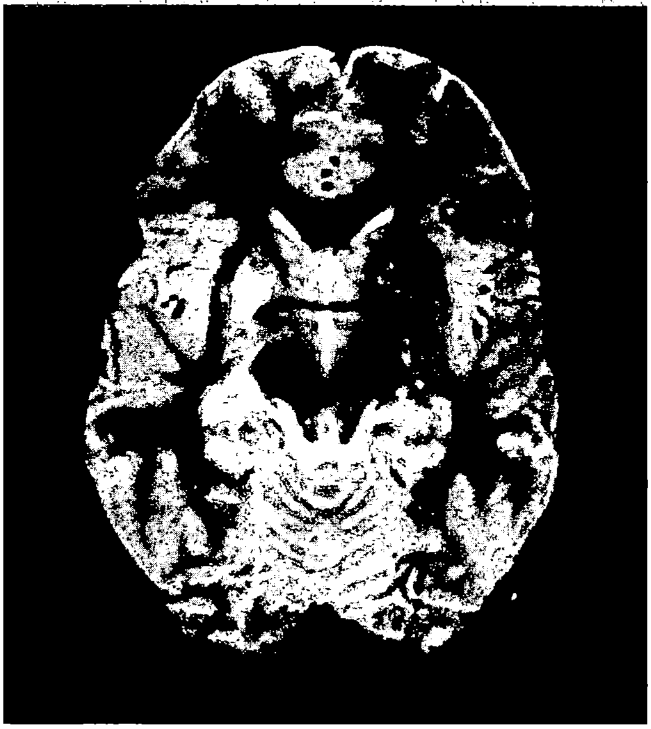
Therapy with steroids, aspirin, or dipyridamole was attempted in three patients (patients 1, 4, and 5). The first patient was treated with steroids, because the arteriographic picture was interpreted as suggesting arteritis. No therapeutic benefit was observed in any of these patients during the study. Follow-up examinations were performed in all patients between 5 and 8 weeks after the onset of the hemiparesis and revealed nearly complete resolution of the neurologic deficits in all but patient 1. One year after onset, no deficits could be detected. None of the patients has had a second episode of hemiparesis to date.

COMMENT

The clinical features of these five patients closely resemble those of the previously described six patients with delayed hemiparesis following primary VZV infection. The mean age of the 11 patients was 4.2 years, and the mean interval from primary VZV infection to the onset of the hemiparesis was 6.3 weeks. Eight of the 11 patients had left-sided hemiparesis (four of six in the previous reports and four of five in our series). All but two of the 11 patients had primarily large-vessel involvement, resulting in ischemia of the deep structures of the affected hemisphere.

The computed tomographic scan was not as sensitive as the MRI scan in documenting the location and extent of the ischemic lesion. Only one arteriogram was abnormal; however, it suggested that vasculitis/vasculopathy was the underlying pathologic mechanism for this condition, confirming the findings of previous reports.[4] Electroencephalography, cerebrospinal fluid examination, hematologic studies, and echocardiography are useful only as a means of eliminating other pathogenic possibilities.

Although six patients have been previously described, to our knowledge, no information is available in the literature concerning outcome in this condition. The patients in this series all did well despite large lesions seen on MRI scans. All of our patients had return of function at the time of subsequent examination. It is possible that the lesions were less extensive than originally believed from MRI scan interpretation due to some edema of tissues sur-



T_2-weighted magnetic resonance image of the brain of patient 4. Note the area of increased signal intensity involving the putamen and internal capsule on the right side.

rounding the ischemic area. Convalescent MRI scans to document the ultimate extent of the lesions were not obtained. The observation that all of these patients recovered premorbid function will be helpful in evaluating the effectiveness of possible therapies that might be suggested in the future. The fact that we were able to accumulate five patients during a period of 14 months suggests that there is a selection bias unknown to us or that this condition is more common than generally recognized.

A number of different pathogenic mechanisms have been proposed for the various neurologic conditions associated with varicella infections in humans. These mechanisms range from direct viral invasion of the brain in the primary infection to autoimmune responses to antigens exposed as a result of tissue injury due to virus in postinflammatory leukoencephalopathy. The mechanism of delayed contralateral hemiparesis following herpes zoster ophthalmicus, namely, vasculopathy caused by the contiguous spread of the herpes zoster virus to the cerebral vessels, has been well documented.[2,6,7] The suggested mechanism of delayed hemiparesis following primary VZV infection is also that of a cerebral vasculopathy.[4] Direct spread from contiguous structures via the ophthalmic nerve has been proposed, as has hematogenous spread of virus.[4,6-8] The predilection for cerebral thrombosis and the predominance of involvement of the large vessels of the cerebral hemisphere are unexplained. This selective involvement resembles that seen in Moya Moya disease, and the mechanisms involved in the two disorders may be similar. Suzuki and Takaku[9] and Suzuki[10] demonstrated, in animal models, that stimulation of the superior cervical ganglion would predispose the carotid artery on that side to vasculopathy induced by circulating immune complexes. This phenomenon could be blocked by ganglionectomy. According to Suzuki and Takaku,[9] in Moya Moya disease, stimulation of the sympathetic nerves because of intense acute, recurrent, or chronic inflammation of the head and face predisposes to arterial thrombosis on the ipsilateral side. The nature of the stimulus to the sympathetic nerves appears to be nonspecific, however, and might include toxins, such as a wasp sting.[11] This sympathetic stimulation combined with the production of systemic antibodies and antigen-antibody complexes might then result in an vasculopathy with thrombus formation.[10] In the patient with primary VZV infection, the primary lesions (chickenpox) provide the stimulation of the superior cervical ganglion either because of intense local irritation or by providing a direct route for the VZV (with a known propensity to produce a retrograde infection of peripheral nerve) to involve the cervical sympathetic ganglion. The delay between the onset of the primary VZV infection and the onset of the hemiparesis is consistent with the time required for the development of the circulating antigen or antigen-antibody complexes that are necessary to induce vasculopathy and thrombus formation in the affected artery. Primary VZV infection thus provides the combination of local and systemic factors required for the development of cerebral thrombosis in these previously healthy children.

We conclude that primary VZV infection with delayed-onset hemiparesis may be more common than has been recognized, typically affecting young children 3 to 8 weeks after primary VZV infection. Magnetic resonance imaging is the most sensitive neuroimaging tool in these children. Prognosis is good, with recovery of function and no recurrences in our patients. The innervation of the carotid artery and the characteristics of the VZV itself combine to provide the local and systemic factors that may trigger the vasculopathy responsible for this syndrome.

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Screening for Behavioral and Emotional Problems in Children and Adolescents With Congenital or Acquired Limb Deficiencies

James W. Varni, PhD, Yoshio Setoguchi, MD

• Children with chronic physical handicaps have been found to be at risk for psychological and social adjustment problems. Accurately identifying in a timely manner those physically handicapped children who are functioning at clinically significant levels of maladjustment may aid in preventing further psychosocial morbidity. The parents of 111 children and adolescents with congenital/acquired limb deficiencies completed the Child Behavior Checklist as a screening instrument to facilitate the identification of behavioral and emotional problems and social incompetence. Based on normalized *T* scores, the children manifested significantly greater behavioral and emotional problems and lower social competence than the normative community sample. Twenty-three percent of the children were reported to function in the clinically significant maladjustment range for behavioral and emotional problems; 14% were reported in the social maladjustment range. Correlations between parent report and child, adolescent, and teacher reports of adjustment ranged from *r* values of .23 to .41. The findings are discussed in terms of the "new hidden morbidity" in pediatric practice.

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Most limb deficiencies in children are congenital in origin, with acquired amputation due to disease or physical trauma being less prevalent.[1] Although children with chronic physical handicaps have been shown to be at increased risk for behavioral and emotional problems,[2,3] the variability observed in adaptation suggests wide individual differences.[3] This at-risk status in combination with the observed individual variance in adaptation indicates the need to identify accurately those physically handicapped children who are functioning at clinically significant levels of maladjustment.

The prevalence of behavioral and emotional problems among children seen in pediatric primary care has been estimated at 16%,[4] whereas the overall prevalence estimates of moderate to severe disorder from epidemiological studies range from 14% to 20%.[5] These observed rates of psychological maladjustment have resulted in the concern for screening children in need of mental health services seen in pediatric primary care.[6] Clearly, the need for screening physically handicapped children for behavioral and emotional problems is no less great, and arguably is even greater given their at-risk status.[2,3]

Similar to laboratory tests for biological disease, identifying psychosocial morbidity in a patient population requires a standardized test with established reliability and validity. However, even when such a test exists, for the test to be ordered there must first be the recognition that the patient population is at increased risk for dysfunction. The clinical decision-making process in ordering a laboratory test is often initiated by patient or parent report of signs and symptoms indicative of potential dysfunction. While such a system of practice seems to work reasonably well for biological disease,[7] there are a number of reasons why it is inadequate for identifying behavioral and emotional problems in children.

In a study screening for behavioral and emotional problems in children 7 to 11 years of age attending pediatric primary care clinics in a health maintenance organization, parents completed the Child Behavior Checklist (CBCL) as the screening instrument.[8] Approximately 25% of the children were identified by the CBCL as maladjusted, and 95% of those identified children and their parents were given a detailed standardized assessment interview. Based on the standardized interview with the parent in this subsample, 11.8% of the children were diagnosed as maladjusted. In contrast, pediatricians diagnosed one or more behavioral and emotional problems in 5.6% of the children during the primary care visit. The pediatricians' clinical assessments of behavioral and emotional problems were highly specific (true-negative rate) in that 84% of children assessed as not maladjusted had no psychological disorder. In contrast, the pediatricians' assessments showed low sensitivity (true-positive rate) in that only 17% of the children with behavioral or emotional problems were identified, resulting in 83% of the cases being incorrectly identified (ie, 83% "hidden morbidity rate"). Costello et al[8] termed this continuing underiden-

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tification of behavioral and emotional problems in standard pediatric practice as the "new *hidden* morbidity," in contrast to the previous term, "new morbidity."[4,6] Thus, the concern is "the extent to which the new morbidity is still a hidden morbidity."[8(p416)]

There are a number of reasons for pediatricians' underidentification of behavioral and emotional problems in children,[9] including limited training in behavioral pediatrics during residency and the difficulty of assessing psychological maladjustment during the brief office visits characteristic of pediatric practice (estimated at 10.7 minutes per visit[10]). It seems reasonable to expect that the underidentification of behavioral and emotional problems in pediatric primary care is also true in pediatric tertiary care for physically handicapped children.

Consequently, the objective of this study was to investigate the CBCL as a screening instrument for behavioral and emotional problems in children and adolescents with congenital or acquired limb deficiencies. It was our intent to compare the findings on children and adolescents with limb deficiencies with standardized scores based on the CBCL normative community sample, as well as to examine the concordance between parent report on the CBCL with child report, adolescent report, and teacher report of behavioral and emotional problems. Based on the previous literature,[11] it was expected that the concordance between parent report with child, adolescent, and teacher report would be in the small ($r = .20$) to medium ($r = .50$) effect size range as statistically defined by Cohen.[12] In the case of bivariate correlation, the effect size is a standardized measure of the magnitude of association between two variables.[12] Furthermore, given previous findings with the CBCL with other pediatric chronic handicaps,[2,3] we expected to find greater behavioral and emotional problems and lower social competence in children and adolescents with limb deficiencies in comparison with the standardized normative community sample of nonhandicapped children and adolescents.

SUBJECTS AND METHODS

Subjects

Subjects were accrued from the Child Amputee Prosthetics Project at the UCLA Department of Pediatrics. To be included in the study, participants had to be English-speaking children, with congenital or acquired limb deficiencies, 6 to 17 years of age. One hundred twenty-three patients were identified for the research project by systematic review of the Child Amputee Prosthetics Project's weekly clinic schedules. Nine families chose not to participate because of time constraints, and missing data precluded the inclusion of three additional families. One hundred eleven children participated in the study (61 boys and 50 girls), typically as part of their routine annual evaluations. The mean (±SD) age of the children was 10.4±3.49 years, with a range of 6 to 17 years. Ninety-two children had congenital limb loss, and 19 had acquired limb loss. The mean family socioeconomic status based on the Hollingshead[13] four-factor index was (mean±SD) 43.2±11.3, indicating on average a middle-class family socioeconomic status.

Screening Instrument

The construct of behavioral and emotional problems was measured by the CBCL–Parent Report Form.[14] The CBCL consists of 118 behavior problem items and 20 social competence items. For the behavior problem items, the parents are instructed to circle the number, 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true), that best describes their child currently or within the past 6 months for the specific symptom listed. Standardized scores for internalizing (eg, depression, anxiety, withdrawal) and externalizing (eg, acting out, aggression) dimensions of behavior problems, and social competence (interpersonal relationships, school performance, activities involvement), are provided. Cutoff points on the distributions of Total Behavior Problems and Social Competence scores have yielded good separation between children referred to mental health clinics and community nonreferred samples.[14] In the CBCL standardization sample, intraclass correlations were in the .90s for interparent agreement, 1-week test-retest reliability, and inter-interviewer reliability. Across all demographic groups, referral status (mental health clinic–referred children vs randomly selected community nonreferred children) accounted for more variance in Total Behavior Problems and Social Competence scores than any other demographic factor (age, sex, race, socioeconomic status).[14] Normative data, stratified for three age groups (4 to 5, 6 to 11, and 12 to 16 years) and sex, are available for 1300 community non–clinic-referred and 2300 mental health clinic–referred children between the ages of 4 and 16 years. The composite Total Behavior Problems scale was used given that it includes all 118 behavior problems items and is standardized for all sex and age groups. The same holds true for the 20 items of the composite Total Social Competence summary scale. Thus, the analyses of behavioral and emotional problems and social competence are based on the two summary scales across all ages and sex. With standard procedures and available norms,[14] scores on all scales were computed as normalized *T* scores. Like ordinary *T* scores, normalized *T* scores have a mean of 50 and an SD of 10, but they are based on the percentile of the distribution of raw scores in such a way as to transform abnormal distributions into normal ones.

Concomitant Measures

Child/Adolescent Report.—The construct of depressive symptoms in children was measured by the Children's Depression Inventory.[15] The construct of depressive symptoms in adolescents was measured by the Beck Depression Inventory.[16] The Children's Depression Inventory and Beck Depression Inventory are the most widely utilized measures of depressive symptoms in children and adolescents and have available considerable normative data from psychiatric, pediatric, and school-based population samples. Each inventory has been shown to be reliable and valid and is self-administered. Only children 8 years of age and older completed these self-report measures.

The construct of trait anxiety in children was measured by the State-Trait Anxiety Inventory for Children.[17] The construct of trait anxiety in adolescents was measured by the State-Trait Anxiety Inventory.[18] Both inventories are the most widely utilized measures of anxiety in children and adolescents, with considerable reliability and validity across diverse populations. Given its greater stability, the trait form was used. Each inventory is self-administered. Only children 8 years of age and older completed these self-report measures.

Teacher Report.—The constructs of behavioral and emotional problems and social competence as reported by the children's and adolescents' teachers were measured by the CBCL–Teacher Report Form.[19] The Teacher Report Form has been well standardized and parallels the CBCL–Parent Report Form, with excellent reliability and validity coefficients. Only teachers of school-age children completed this questionnaire.

Degree of Limb Loss.—As part of the overall Child and Adolescent Needs Project at the UCLA Child Amputee Prosthetics Project, we developed the Degree of Limb Loss Scale. Upper-body limb loss was scored as follows: forequarter, 8; shoulder disarticulation, 7; above elbow, 6; elbow disarticulation, 5; below elbow, 4; wrist disarticulation, 3; transcarpal/metacarpal, 2; and partial hand, 1. Lower-body limb loss was scored as follows: hemicorporectomy, 9; hemipelvectomy, 8; hip disarticulation, 7; above knee, 6; knee disarticulation, 5; below knee, 4; ankle disarticulation, 3; transtarsal, 2; and partial foot, 1. Complete/partial phocomelia and proximal femoral focal deficiency were scored using the above scale according to the length of the limb. Total limb loss was calculated as the sum of the upper- and lower-limb loss ratings.

Procedure

Parents were informed of the study when scheduling a regular clinic appointment. If they agreed to participate, a packet containing more information about the study, an informed consent form, and half of the study questionnaires were mailed home. Just before the scheduled clinic appointment, the parents were contacted by phone and asked to remember to return the completed questionnaires with them. The child and parent were met by a research assistant when they arrived at the clinic. The signed consent form was obtained, as well as verbal assent from the child. Both parent and child consent were required for study inclusion. They were then asked whether they had any questions before completing the remaining questionnaires. Total estimated time to complete all the questionnaires at home and at the clinic individually by the children and parents was 60 minutes each. The CBCL takes approximately 15 minutes to complete. The Institutional Review Board at UCLA approved this research protocol.

RESULTS

Average Adjustment

The mean *T* scores for these children on the CBCL were (mean±SD) 56±9.96 on the Total Behavior Problems scale and 48±10.51 on the Total Social Competence scale. The distribution for the Total Behavior Problems scale was essentially normal and not markedly influenced by extreme scores. Skewness (0.188) and kurtosis (−0.659) were minimal for the Total Behavior Problems scale, and the median was within 1.5 points of the mean, suggesting a normal distribution of scores. For the Total Social Competence scale, although the median was within 1 point of the mean, skewness (−1.23) and kurtosis (3.30) indicate a more peaked than normal distribution of values around the mean, with a tail toward lower Total Social Competence scale values.

Based on the *T* scores, the average child with limb deficiency in this cohort manifested more behavioral and emotional problems than 72% of children in the normative community sample.[14] Furthermore, the social competence of the average child with limb deficiency was described as lower than that of 58% of the children in the normative community sample.

Prevalence of Maladjustment

The recommended cutoff points for clinical maladjustment on the CBCL are a *T* score more extreme than the 90th percentile on the Total Behavior Problems scale and the 10th percentile on the Total Social Competence scale in comparison with the normative community sample.[14] This translates to a *T* score above 63 for the Total Behavior Problems scale and a *T* score below 37 for the Total Social Competence scale. Based on these cutoff scores, 23% of the children with limb deficiencies manifested behavioral and emotional maladjustment, and 14% manifested social maladjustment. The expected proportion of maladjustment in the general population would be 10% as derived from the CBCL cutoff points based on the normative community sample standardized scores.

Relationship to Demographic Variables

The Total Behavior Problems scale was not significantly correlated with age ($r[111]=.06$), sex ($r[111]=.14$), socioeconomic status ($r[109]=-.02$), or degree of limb loss ($r[111]=-.10$). The Total Social Competence scale was also not significantly correlated with age ($r[111]=-.01$), sex ($r[111]=-.07$), socioeconomic status ($r[109]=.07$), or degree of limb loss ($r[111]=.06$).

Comparison With Normative Samples

We calculated *z* tests[20] between the Total Behavior Problems scale mean and the normative community sample mean. The children with limb deficiencies manifested significantly more behavioral and emotional problems than the normative community sample ($z=6.0$, $P<.001$). For the Total Social Competence scale, the children with limb deficiencies exhibited less social competence than the normative community sample ($z=-3.2$, $P<.001$).

Correlations Between Parent Report and Child, Adolescent, and Teacher Reports

The parent report of behavioral and emotional problems on the CBCL Total Behavior Problems scale was significantly correlated with child report of depressive symptoms ($r[54]=.40$, $P<.01$) and trait anxiety ($r[52]=.41$, $P<.01$), adolescent report of depressive symptoms ($r[33]=.35$, $P<.05$), and teacher report of behavioral and emotional problems on the CBCL–Teacher Report Form ($r[79]=.29$, $P<.05$). The correlation between adolescent report of trait anxiety and parent report was not statistically significant ($r[34]=.23$, $P<.10$). There was a significant correlation between the parent and teacher reports of social competence on the parallel CBCL Total Social Competence scales ($r[79]=.24$, $P<.05$).

COMMENT

The results of this study suggest that the CBCL may be a useful screening instrument in identifying behavioral and emotional problems and social incompetence in children and adolescents with limb deficiencies. While no available screening instrument can be considered the "gold standard," the CBCL is the most widely utilized assessment questionnaire for screening for behavioral and emotional problems and social incompetence in epidemiological studies.[2,3,5,8,21,22]

The pattern of results between parent report and child, adolescent, and teacher reports are consistent with previous studies of cross-informant concordance.[11] As hypothesized, the obtained correlations were in the small ($r=.20$) to medium ($r=.50$) effect size range.[12] The effect size of the observed correlations supports the need for a two-stage screening process where the CBCL can be utilized as an efficient first-stage screening instrument, followed by more symptom-specific assessment when behavioral and emotional problems are evident during the initial screening.[5,21] While parents seem to identify accurately externalizing behavior problems (aggression, acting out, hyperactivity), they often underidentify their children's (and to a greater extent their adolescent's) internalizing behavior problems (depression, anxiety, withdrawal).[11] Consequently, when using the CBCL as a screening instrument, parent report of internalizing behavior problems might warrant a lower cutoff point than externalizing behavior problems. The small correlations between parent and teacher reports indicate the importance of screening from the two most significant environments of the child and adolescent, ie, the home and the school settings.[11,21] For practical and logistical reasons, a two-stage screening process can be implemented where the CBCL–

Teacher Report Form is administered if the CBCL–Parent Report Form suggests school-related difficulties.

Previously, we found that there are a number of potentially modifiable predictors of the psychological adaptation of children with limb deficiencies that may give direction to intervention efforts.[23-28] These empirical investigations further underscore the value of screening for behavioral and emotional problems by suggesting the potential modifiable nature of the observed psychosocial morbidity seen in these children.[29] Accurate identification of behavioral and emotional problems in a timely manner may reasonably lead to expectations of viable mental health interventions that may serve to prevent further psychosocial morbidity as well as to remediate existing maladaptation.[4] Costello and Pantino[4(p289)] cogently summarize the need for accurate identification of children's behavioral and emotional problems:

> It could be argued that many of these problems are transitory, and that the child will "grow out of it," given a course of benign neglect. Such data as exist show that, although there is no evidence that a given disorder in childhood predicts the same disorder in adulthood, disturbed children are much more likely to become disturbed adults than are nondisturbed children. In any case, children's problems demand to be treated for their own sake, irrespective of their long-term implications, if they cause the child suffering.

Even when children are suffering emotionally, they rarely are in the position to refer themselves for treatment.[30] Parent report of their child's symptoms remains the primary means for pediatricians to identify psychosocial morbidity in their patients. One partial explanation for the general underidentification of behavioral and emotional problems in pediatric primary care derives from studies of parental concerns during clinic visits. In one study, only 30% of mothers were most worried about their child's physical health. The remaining 70% were most concerned about problems of parenting, behavior, psychosocial development, discipline, mental development, mother-child interaction, adjustment to divorce and other life changes, and adolescent transition.[31] However, only 28% of these mothers had discussed these concerns with their pediatrician. Explaining their failure to communicate their concerns regarding behavioral and emotional problems, the mothers said they were unaware that their pediatricians would help, or they questioned their pediatricians' ability or interest to assist them with these concerns. In another study, 81% of the questions that parents wished to direct to their pediatricians, given sufficient time, were concerned with psychosocial issues.[32]

Together, these studies suggest that parent-perceived pediatrician lack of interest and time during a routine primary care visit may serve as barriers to the communication of parental concerns of child behavioral and emotional problems. We suggest that utilizing a screening instrument such as the CBCL, which can be completed by the parent before the visit in the waiting room or previously at home, may help overcome these barriers to the accurate identification of children in need of mental health services. By discussing the completed CBCL with the parent during a routine clinic visit on an annual or biannual basis, a cost-efficient and practical mechanism exists to uncover the "new *hidden* morbidity" so as to provide truly comprehensive care to children and adolescents with chronic physical handicaps.

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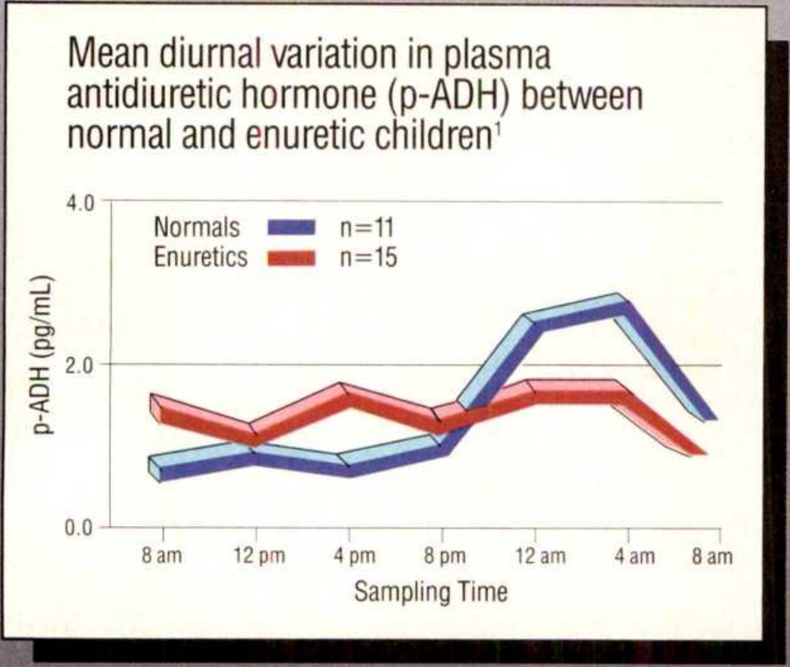

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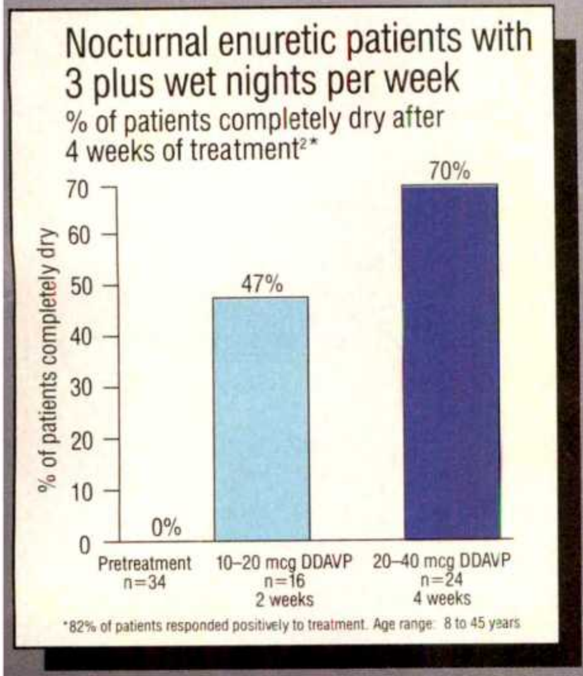

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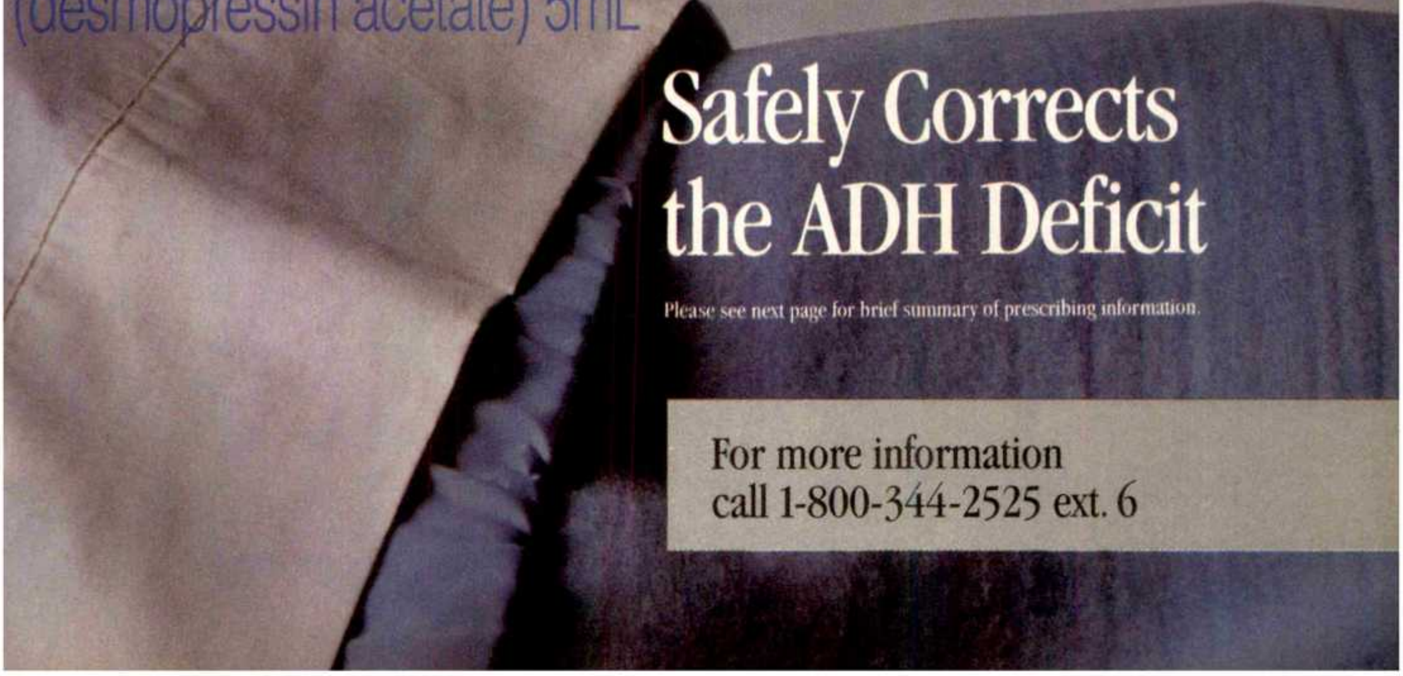

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PRECAUTIONS:

General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=59) %	DDAVP 20 mcg (N=60) %	DDAVP 40 mcg (N=61) %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information. Rev. 6/89

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International Conference on Child Day Care Health:

Science, Prevention, and Practice

June 15–17, 1992
Atlanta, Georgia USA

Call for Abstracts

A conference entitled the **"International Child Day Care Health: Science, Prevention, and Practice,"** will be held at the Hotel NIKKO Atlanta, Atlanta, Georgia on June 15-17, 1992. The objective of this conference is to provide structured and informal opportunities to exchange information, skills, knowledge, and experiences related to child day care health. Presentations and discussion will focus on three major themes: (1) Child Day Care Health; (2) Meeting the Needs of Children and Care Givers; and (3) Translating Science into Practice. Submissions are encouraged for concurrent scientific sessions on infectious diseases; injuries and hazards; health promotion; children with special needs and disabilities; environmental health; developmental and psychological aspects; occupational health; impact of regulations, standards, accreditation, and training; and economics. The abstract deadline is January 15, 1992. For more information contact Lillian Glickman at Pace Enterprises, Inc. at (404) 633-8610 or FAX (404) 633-8745.

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SPECIAL FEATURE

Pathological Case of the Month

Lewis Barness, MD (Contributor), *Enid Gilbert-Barness, MD* (Contributor and Section Editor)

A 16-year-old girl was admitted to the hospital with jaundice of 2 weeks' duration. She appeared well until age 14 years, when she developed a tremor, the cause of which was not determined. Menarche occurred at age 15 years.

On admission, she was markedly jaundiced and extremely lethargic. She was intermittently incoherent and had a persistent tremor. The liver edge was palpable 4 cm below the right costal margin, and the liver span was 12 cm. Ascites was present.

See also p 22.

Laboratory values were as follows: hemoglobin, 60 g/L; serum albumin, 10 g/L; serum ammonia, 235 μmol/L; serum alanine aminotransferase, 800 U/L; aspartate aminotransferase, 600 U/L; γ-glutamyl transferase, 800 U/L; and prothrombin time, 34 seconds. Results of tests to detect hepatitis A, B, and C were negative.

A diagnosis of fulminant hepatitis with cirrhosis was made. After additional tests, a liver transplant was performed. The gross appearance of the liver is shown in Fig 1, and microscopic sections are shown in Figs 2 and 3.

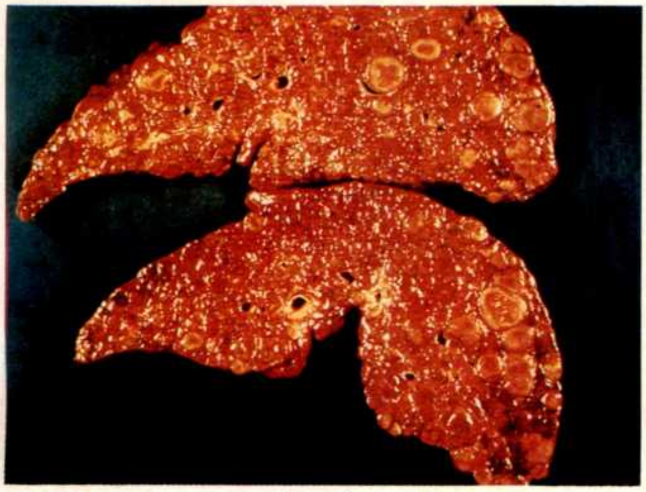
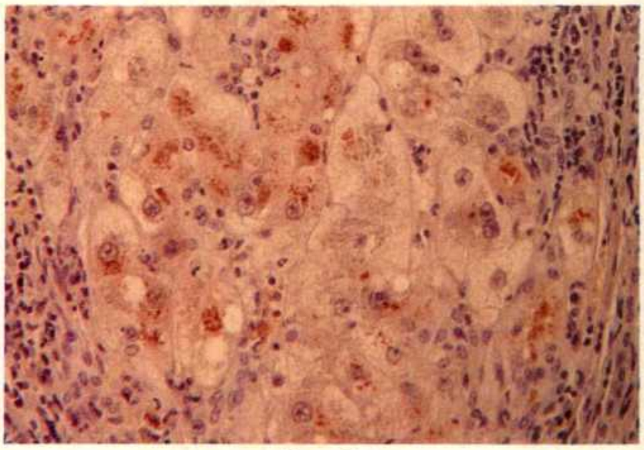


Figure 1.



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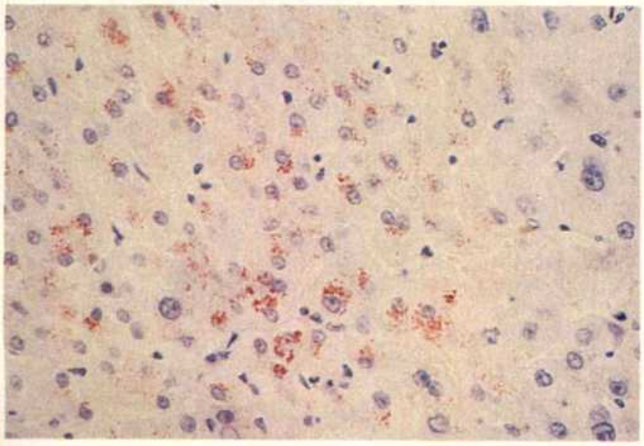

Figure 3.

The Editors welcome contributions to Pathological Case of the Month, Picture of the Month, *and* Radiological Case of the Month. *Those who wish to contribute should send their manuscripts to Dr Gilbert-Barness* (Pathological Case of the Month), *Departments of Pathology and Pediatrics, University of Wisconsin, Center for Health Sciences, E5/326, 600 Highland Ave, Madison, WI 53792; Dr Tunnessen* (Picture of the Month), *The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104; or Dr Wood* (Radiological Case of the Month), *Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Accepted for publication October 18, 1991.

Contributed from the Departments of Pathology and Pediatrics, University of Wisconsin, Center for Health Sciences, Madison.

Reprint requests to Departments of Pathology and Pediatrics, University of Wisconsin, Center for Health Sciences, E5/326, 600 Highland Ave, Madison, WI 53792 (Dr Gilbert-Barness).

Diagnosis and Discussion

Wilson's Disease (Hepatolenticular Degeneration)

Fig 1.—*Macronodular and micronodular cirrhosis of the liver.*

Fig 2.— *Low-power microscopic view of the liver showing cirrhosis inflammation, ballooning of hepatocytes, glycogenated nuclei, and pigment in cells (hematoxylin-eosin, original magnification ×250).*

Fig 3.—*Rhodanine stain demonstrates the presence of copper (original magnification ×100).*

This girl had not been carefully examined in the past. Additional laboratory values included the following: serum ceruloplasmin, 1000 mg/L; serum copper, 400 µmol/L; and serum haptoglobin, 0 g/L. She also had bilateral Kayser-Fleischer rings. If she had been examined and diagnosed earlier, even as late as age 14 years, when psychiatric and neurologic symptoms appeared, she may have responded to chelation therapy, and liver transplantation may have been avoided. In addition to the presence of Kayser-Fleischer rings, increased urinary excretion of copper after administration of one dose of penicillamine is strongly suggestive of hepatolenticular degeneration.

The basic defect in Wilson's disease has not been elucidated. The pathologic effects on the liver, kidneys, and brain are considered to be directly related to the accumulation of copper ions.

In the precirrhotic stage of Wilson's disease, the changes resemble a chronic, active hepatitis with focal necrosis, scattered acidophilic bodies, and moderate to marked steatosis.[1] Glycogenated nuclei in periportal hepatocytes are a typical finding in Wilson's disease. Kupffer's cells are hypertrophied and may contain hemosiderin. In later stages, periportal fibrosis, portal inflammation, and, finally, cirrhosis occur.

Submassive or massive hepatocellular necrosis can occur with Wilsons' disease. The clinical and biochemical findings in such cases may resemble those of chronic active hepatitis.[1-4]

The cirrhosis of Wilson's disease is macronodular or macronodular and micronodular, with periportal fibrosis, cholangiolar proliferation, and lymphocytic infiltration.[5]

The presence of copper may not be cytochemically demonstrable in the precirrhotic stage. In young, asymptomatic patients, the copper is diffusely distributed in the cytoplasm but later accumulates in lysosomes.[6] Rhodamine and rubeanic acid stains specifically detect the presence of copper.[7,8] Copper-associated protein can be stained with orcein or aldehyde fuchsin.[9,10]

The ultrastructural changes in Wilson's disease are pathognomonic.[1,11,12] The mitochondria show marked pleomorphism, intracristal spaces widen, and microcysts form at the tips of the cristae.[11] Copper deposits are extremely electron dense.

A recent study[13] has shown that a major copper-binding protein in Wilson's disease is metallothionein. It has been suggested that the liver damage in Wilson's disease may be due to the toxic ionic form of copper, which saturates the binding sites of metallothionein.[13]

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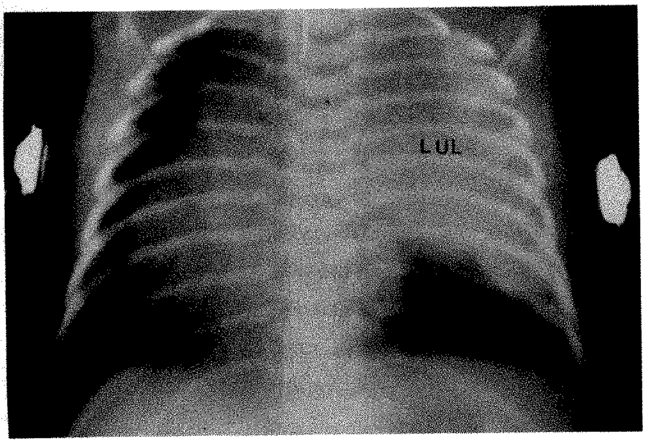
SPECIAL FEATURE

Radiological Case of the Month

Ashima Madan, MD, Marguerite Parisi, MD (Contributors); *Beverly P. Wood, MD* (Section Editor)

This newborn girl was the 2620-g product of an uncomplicated twin gestation and was born at 38 weeks' gestation via spontaneous vaginal delivery. Her Apgar scores were 6 at age 1 minute and 7 at age 5 minutes. At birth, she was mildly cyanotic and tachypneic. Results of physical examination revealed a harsh, grade 3/6 systolic ejection murmur with diastolic radiation over the right-lower sternal border. The lungs were clear to auscultation. The infant underwent intubation soon after birth because of increasing respiratory distress, underwent extubation at age 24 hours, and was weaned to room air at age 48 hours.

A frontal roentgenogram of the chest (Fig 1) and a computed tomogram of the chest with intravenous contrast enhancement (Fig 2) were obtained at age 1 day. Serial chest roentgenograms were obtained at ages 2, 3, and 6 days (Fig 3).



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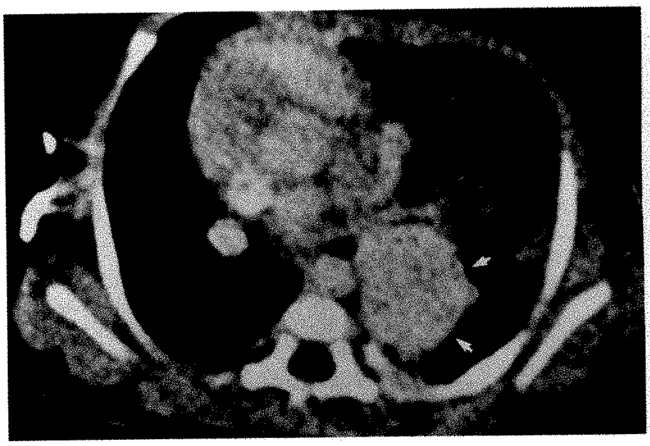

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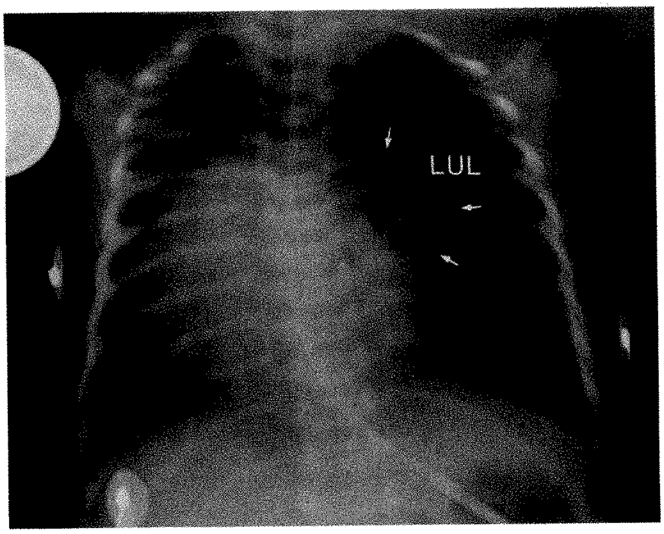

Figure 3.

Accepted for publication August 15, 1991.

Contributed from the Departments of Pediatrics (Drs Madan and Parisi) and Radiology (Dr Parisi), University of California at San Francisco.

Reprint requests to Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Denouement and Discussion

Absent Pulmonic Valve Presenting With Congenital Lobar Emphysema

Fig 1.—*Frontal roentgenogram of the chest showing fluid density of the left upper lobe (LUL), causing the enlarged heart and mediastinum to shift to the right. The mass represents lobar emphysema of the left upper lobe with retained alveolar fluid.*

Fig 2.—*Computed tomographic scan of the chest during administration of the intravenous contrast medium shows a 5-cm mass (arrows) that enhances in the left hilar region, representing a pulmonary artery aneurysm. The left upper lobe is enlarged. The left-upper-lobe bronchus is not defined and is obstructed by the pulmonary artery aneurysm.*

Fig 3.—*Frontal roentgenogram of the chest at age 6 days shows aeration and hyperinflation of the left upper lobe (LUL). The convex mass (arrows) in the left hilar region is an aneurysm of the main and left pulmonary arteries.*

The infant underwent intubation soon after birth because of increasing respiratory distress and later developed congestive heart failure. Aneurysmal dilatation of the main and left pulmonary arteries; a dysplastic, incompetent pulmonic valve; pulmonary stenosis; atrial and ventricular septal defects (ASD and VSD); and patent ductus arteriosus were demonstrated with echocardiography and cardiac catheterization at age 9 days.

At age 3 months, she underwent surgical closure of the ASD and VSD. After surgery, oxygenation was inadequate and the infant underwent a left-upper-lobe excision and repair of the pulmonary artery aneurysm. She developed cardiac tamponade and, despite adequate resuscitative measures, experienced cardiac arrest and died.

Absence of the pulmonic valve, with or without associated congenital cardiac anomalies, is a rare and often fatal condition. First described by Cheevers[1] in 1847, it usually occurs in association with a VSD, pulmonic obstruction (tetralogy of Fallot), pulmonary insufficiency, and aneurysmal dilatation of the pulmonary arteries. It has been suggested that the aneurysmal dilatation of the pulmonary arteries results either from congenital weakness at the base of the pulmonary artery or from the hemodynamic consequences of a VSD and infundibular stenosis in conjunction with severe pulmonary regurgitation.[2]

The presenting signs and symptoms vary, but include cyanosis and a harsh systolic murmur with a characteristic to-and-fro quality. The initial cyanosis usually resolves by age 1 week because of a decrease in pulmonary vascular resistance.[3] Chest roentgenography characteristically shows an enlarged heart with dilated main and left pulmonary arteries[4] and consequent lobar hyperexpansion on the left.

Pulmonary complications are common, with respiratory distress apparent on physical examination and emphysema evident with chest roentgenography. D'Cruze et al[5] were the first to stress the importance of respiratory obstruction in patients with congenital absence of the pulmonic valve. In the neonate, bronchial cartilage is soft, pliable, and easily compressed by adjacent structures—in this case, the aneurysmally dilated main and left pulmonary arteries. Providing supportive evidence for this hypothesis, Stanger et al,[6] in a review of 140 cases of lobar emphysema, noted that 28 cases were associated with congenital cardiac disease.

Despite a variety of therapies, appropriate management remains controversial, and mortality, especially in patients with pulmonary complications, remains high. Conservative medical management alone results in extremely high mortality (76%). Surgical intervention decreases the mortality rate to 41.3%.[3] Surgical alternatives include: (1) correcting the cardiac defect alone as an attempt at resolving the associated pulmonary abnormality, (2) performing a lobectomy (if severe lobar emphysema is present) with subsequent correction of the cardiac defect, or (3) treating both the cardiac and pulmonary abnormalities simultaneously.[7] Corrective intracardiac surgery consists of closure of the VSD and relief of the pulmonary outflow tract obstruction with placement of a transannular patch[8] and a prosthetic pulmonary valve.[9] Palliative surgery has been attempted with aneurysmorraphy and suspension of the pulmonary artery from the retrosternal fascia or with resection of the artery and subsequent graft replacement.[10,11]

Like Osman et al,[4] we believe that characteristic clinical and roentgenographic features accompany congenital absence of the pulmonic valve. Awareness of this anomaly and its associated cardiac and pulmonary manifestations may lead to early diagnosis and, possibly, improved outcome. Contrast-enhanced, dynamic cinecomputed tomography is valuable for diagnosis of secondary bronchial obstruction in the presence of a pulmonary artery aneurysm.

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SPECIAL FEATURE

Picture of the Month

Walter W. Tunnessen, Jr, MD (Contributor and Section Editor)

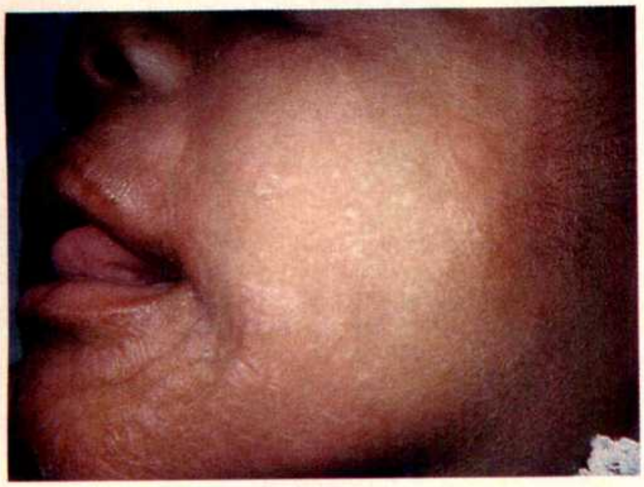

Figure 1.

This 6-week-old infant presented with a low-grade fever, upper-respiratory-tract symptoms, irritability, and a rash.

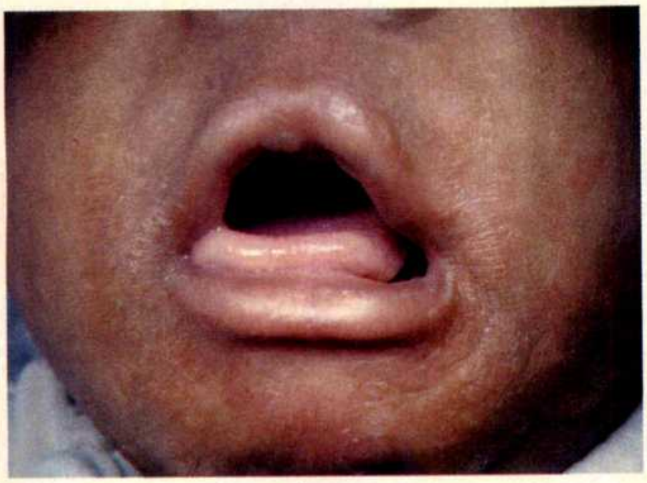

Figure 2.

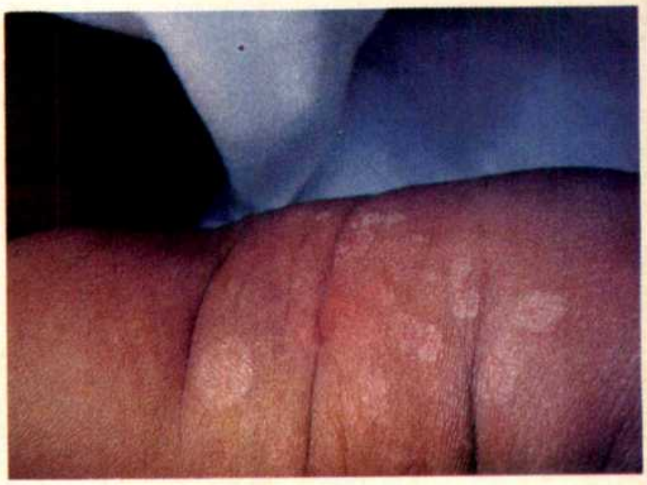

Figure 3.

Accepted March 15, 1991.

Contributed from the Department of Pediatrics, School of Medicine, University of Pennsylvania.

Reprint requests to The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Tunnessen).

Denouement and Discussion

Congenital Syphilis

Figs 1 and 2.—*The perioral lesions are slightly papular and flat topped, while lesions on the cheeks appear dry and slightly scaly.*

Fig 3.—*Ovoid and annular, pink, scaly lesions are present on both upper legs.*

Manifestations

Cutaneous lesions occur in one third to one half of infants with congenital syphilis. The lesions may be relatively inconspicuous, as illustrated by the Figures, or they may be prominent and vesiculobullous or eroded. The most common lesions are round to oval maculopapular or papulosquamous lesions strongly suggestive of pityriasis rosea, one of the common skin disorders that secondary syphilis mimics. The lesions may occur anywhere, but are most common on the face, the extensor surfaces of the arms and legs, and the perineum. Occasionally, the palms and soles are involved. The annular and ovoid lesions are bright pink to red and become coppery over time. The lesions disappear over 1 to 3 months.

Mucous membrane lesions occur in one third of infants with congenital syphilis, especially in the mouth and on the lips. The lesions tend to be small, round, flat-topped papules that appear moist. The lesions may fissure at the mucocutaneous junction around the mouth, creating radiating scars known as rhagades as they heal.

Vesiculobullous and eroded hemorrhagic lesions are relatively uncommon in congenital syphilis. Their appearance on the palms and soles, however, is strongly suggestive of this disorder. The palms and soles may appear macerated, edematous, or indurated. They may also peel and appear dull red and shiny. Flaky desquamation in an acral distribution is present in some cases. The lesions of condyloma lata resemble raised, flat, moist warts and most frequently occur in the anogenital area and around the mouth and nostrils.

Approximately two thirds of infants with congenital syphilis are free of symptoms at birth.[1] Clinical manifestations of the infection usually occur by age 3 to 4 months. Rhinitis (snuffles) is rarely absent in the infant manifesting signs of congenital syphilis. The nasal mucosa becomes swollen, followed by a profuse mucopurulent discharge teeming with spirochetes. The infection may lead to mucosal ulceration and, in some cases, cartilage destruction that eventually results in the saddle-nose deformity.

Hepatosplenomegaly occurs in 50% to 75% of affected infants, and some may have jaundice. Lymphadenopathy may also be prominent. Periostitis is evident in roentgenograms of most affected infants but most infants are not symptomatic. Long-bone involvement with the periostitis may be extremely painful, leading to Parrot's pseudoparalysis. Other clinical manifestations include anemia, fever, irritability, and a hoarse cry.

The increase in reported cases of congenital syphilis is dramatic and frightening. In 1989, a 95% increase in cases compared with 1987 figures was reported to the Centers for Disease Control, representing the highest yearly total of cases reported since the introduction of penicillin.[1] Serologic tests for detection of syphilis should be performed in both mothers and infants in high-risk situations at delivery. Screening will not identify some cases because of recent acquisition of infection and the failure of antibody response. Three of seven infants diagnosed between ages 3 and 14 weeks as having congenital syphilis presented only with fever and were found to have aseptic meningitis as the first manifestation of this infection.[2] Congenital syphilis must again be considered in the differential diagnosis of all febrile infants.

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Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*.
Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These eactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional atal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients reated with ampicillin class antibiotics including *Augmentin*. The significance of hese findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic, hepatocellular, or mixed cholestatic-hepatocellular. Signs/symp-oms may appear during or after therapy and they resolve completely over time.

emic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic urpura, eosinophilia, leukopenia and agranulocytosis have been reported during herapy with penicillins. These reactions are usually reversible on discontinuation f therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis as noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, onfusion, behavioral changes, and/or dizziness have been reported rarely.

osage: Adults: The usual adult dose is one *Augmentin* '250' tablet every ight hours. For more severe infections and infections of the respiratory tract, the ose should be one *Augmentin* '500' tablet every eight hours.

Since both the *Augmentin* '250' and '500' tablets contain the same amount f clavulanic acid (125 mg, as the potassium salt), two *Augmentin* '250' tablets re not equivalent to one *Augmentin* '500' tablet. Therefore, two *Augmentin* '250' tablets should not be substituted for one *Augmentin* '500' tablet for eatment of more severe infections.

hildren: The usual dose is 20 mg/kg/day, based on amoxicillin component, in ivided doses every eight hours. For otitis media, sinusitis and other more severe ifections, the dose should be 40 mg/kg/day, based on the amoxicillin component, i divided doses every eight hours. Also available as *Augmentin* '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult commendations.

RS-AG:L1

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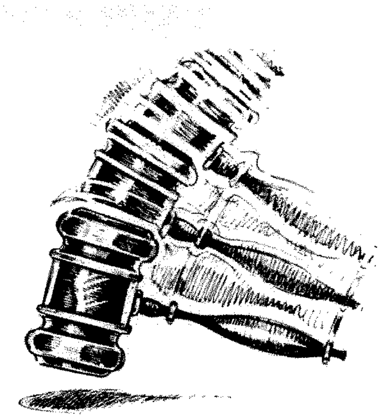

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- Children's Advil® Suspension (10 mg/kg) provides better fever management than Tylenol® (10 mg/kg) in fevers above 102.5°F†[1]
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Please see following page for brief summary of prescribing information.

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Suspension
100mg/5mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risks of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time.

CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions. Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 6 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis, fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coomb's positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (eg., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

* Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children), 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

References:

1. Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989; 46: 9-17.
2. Independent Clinical Studies: Reduction of Fever in Children, Multiple Dose/Single Dose. Data on file, Medical Department, Whitehall Laboratories.
3. Giannini EH, Brewer EJ, Miller ML, et al. Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. *J Pediatr.* 1990;117:645-652.

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Tetralogy of Fallot

The Spectrum of Severity in a Regional Study, 1981-1985

Sharon S. Karr, MD; Joel I. Brenner, MD; Christopher Loffredo, MS; Catherine A. Neill, MD, FRCP (Lon); Judith D. Rubin, MD, MPH

• The combined medical and surgical mortality rate for 125 infants with tetralogy of Fallot registered in the Baltimore-Washington Infant Study from 1981 to 1985 was 28% (mean age at follow-up for living infants, 40 months). Despite early diagnosis and successful early repair in many infants, significant risk factors for death included pulmonary atresia, major additional cardiac anomalies, major noncardiac malformations, low birth weight, and prematurity. There is a wide spectrum of severity, ranging from infants with isolated tetralogy and no risk factors who have an excellent prognosis to infants with three or more risk factors and a high probability of neonatal death. Further treatment advances will improve outcome in some, but not all, infants. A regional all-inclusive study of a specific cardiac defect can define research and treatment challenges not obvious from selected clinical series.

(*AJDC*. 1992;146:121-124)

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart malformation, with a prevalence of 2.5 to 3.5 per 1000 live births.[1] Approximately one fifth of infants with TOF have associated pulmonary outflow atresia, a more severe form of the defect. Recent clinical studies that describe the excellent outcome of surgical repair in early infancy[2-4] do not represent the entire spectrum of TOF as a disorder of ectomesenchymal cell migration, often associated with other congenital defects involving cells arising from the neural crest.[5] We evaluated the entire regional cohort of live-born infants with TOF registered from 1981 to 1985 in the Baltimore-Washington Infant Study (BWIS), in an attempt to define risk factors affecting survival. We hypothesized that there was a spectrum of severity of tetralogy and that poor outcome in some infants would be associated with multiple cardiac and noncardiac risk factors.

SUBJECTS AND METHODS

The BWIS is a population-based etiologic study of congenital cardiovascular malformations (CVMs), the methods of which have been previously described in detail.[6-8] The BWIS was approved by the institutional review boards of all of the participating hospitals; informed consent for interviews and medical record reviews were obtained from parents of all subjects. Among the live births of a defined region (ie, Maryland, the District of Columbia, and northern Virginia), all infants are identified in whom CVM has been confirmed before age 1 year with echocardiography, cardiac catheterization, surgery, or autopsy. Case identification at the six collaborating regional pediatric cardiology centers in Baltimore, Md, Washington, DC, and Fairfax, Va, was supplemented by a "community search" of death certificates and autopsy records for infants with CVM not referred to a center.[9]

From January 1, 1981, through December 31, 1985, the BWIS registered 125 infants who had classic anatomic findings of TOF: large, nonrestrictive, anterior, malaligned, ventricular, septal defect with pulmonic stenosis or atresia and overriding aorta. Infants with atrioventricular septal defect with tetralogy hemodynamics, double-outlet right ventricle, or restrictive ventricular septal defect with pulmonic stenosis or double-chambered right ventricle were not included.

The BWIS registration and 1-year update information provided by the pediatric cardiology referral centers was supplemented with a review of medical records by one of the authors (S.S.K.). The following data were abstracted from the medical records: birth weight, gestational age, race, sex, age at diagnosis, method of diagnosis, additional cardiac and noncardiac diagnoses, date of last medical visit, number of cardiac catheterizations, number and type of surgical interventions, weight and age at surgical repair, and clinical status at follow-up. Cause of death was determined by review of clinical and autopsy records by three of the authors (S.S.K., J.I.B., and C.A.N.). The follow-up period was defined as the infant's age at death or at the last recorded medical visit. The mean (±SD) follow-up for living infants was 40±22 months (range, 1 to 86 months). Selected socioeconomic information (ie, maternal age, education, marital status, and household income) was obtained from the BWIS data set.

Contingency table χ^2 analysis was performed for comparison of survival status (alive or dead at follow-up) with sex, race, birth weight, gestational age, pulmonary atresia status, additional cardiac and noncardiac defects, age at diagnosis, maternal age, maternal education, marital status, and household income. Odds ratios (OR) and 95% confidence limits (CI) were determined for variables significantly associated ($P<.05$) with survival status. A variable adjusting birth weight for gestational age was computed for inclusion in multivariate analyses.[10]

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From the Children's National Medical Center, Washington, DC (Dr Karr); the Departments of Pediatrics (Drs Brenner and Rubin) and Epidemiology and Preventive Medicine (Mr Loffredo and Dr Rubin), University of Maryland School of Medicine, Baltimore; and the Department of Pediatrics, The Johns Hopkins Medical Institutions, Baltimore (Dr Neill).

Reprint requests to the Division of Pediatric Cardiology, University of Maryland Medical System, 22 S Greene St, Room N5W40, Baltimore, MD 21201 (Dr Brenner).

Table 1.—Demographic and Medical Characteristics of Infants With Tetralogy of Fallot by Survival Status

Characteristic	No. (%) of Infants: Alive (n=90)	No. (%) of Infants: Dead (n=35)	*P**
Sex			
M	54 (60.0)	17 (48.6)	.247
F	36 (40.0)	18 (51.4)	
Race			
White	56 (62.2)	20 (57.1)	.508
Black	28 (31.1)	14 (40.0)	
Other	6 (6.7)	1 (2.9)	
Birth weight, g			
<2500	20 (22.2)	16 (45.7)	.009
≥2500	70 (77.8)	19 (54.3)	
Gestational age, wk			
<38	15 (16.7)	19 (54.3)	.001
≥38	75 (83.3)	16 (45.7)	
Small for gestational age			
Yes	18 (20.0)	8 (22.9)	.724
No	72 (80.0)	27 (77.1)	
Pulmonary atresia			
Yes	11 (12.2)	14 (40.0)	.001
No	79 (87.8)	21 (60.0)	
Other cardiac anomalies			
Yes	7 (7.8)	11 (31.4)	.001
No	83 (92.2)	24 (68.6)	
Noncardiac anomalies			
Yes	18 (20.0)	16 (45.7)	.004
No	72 (80.0)	19 (54.3)	
Age at diagnosis, d			
<1	2 (2.2)	4 (11.4)	.015
1-7	41 (45.6)	24 (68.6)	
8-30	17 (18.9)	4 (11.4)	
31-90	18 (20.0)	2 (5.7)	
≥91	12 (13.3)	1 (2.9)	

*χ^2 analysis.

Variables with significant odds ratios for infant death were entered into a Cox proportional-hazards linear regression model as covariates, with survival (in days) as the dependent variable.

RESULTS

Characteristics of the 125 infants with TOF are shown in Table 1 according to survival status.

Demographic Characteristics

The sex and race distributions of the study group were similar to the entire BWIS case population. The mean birth weight was 2855 g. Thirty-six infants (29%) weighed less than 2500 g at birth, 34 infants (27%) were premature, and 25 (20%) of the infants were small for gestational age.

Anatomic Variants

One hundred (80%) of the 125 infants had pulmonic stenosis with right ventricular-pulmonary artery continuity (TOF) and 25 (20%) had associated pulmonary outflow atresia (TOF-PA). A right aortic arch was diagnosed in 21 patients (16.8%). Additional cardiac anomalies were present in 18 patients (14%), including four with absent pulmonary valve, three with coronary artery anomalies, two with aortic valve stenosis, and one each with the following: dysplastic tricuspid and aortic valve, absent right pulmonary artery, quadricuspid aortic valve with single coronary artery, and a sinus of Valsalva aneurysm. Five infants (4%) had pulmonary artery branch stenosis.

Noncardiac anomalies were present in 34 infants (27%). Aneuploidy was present in 10 patients (8%), eight with trisomy 21 and two with trisomy 13. Ten infants (8%) had syndromes; 14 (11%) had gastrointestinal, genitourinary, skeletal, or other malformations.

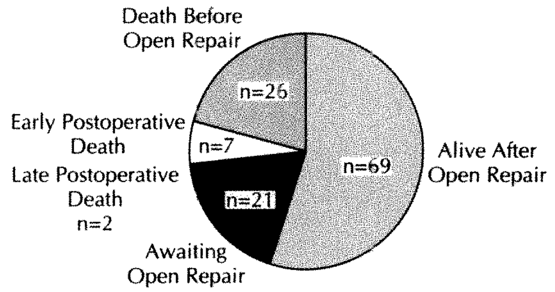

Fig 1.—*Vital status at follow-up of patients with teratology of Fallot.*

Diagnosis and Treatment

Early diagnosis of these patients was achieved, with 71 (56.8%) confirmed by age 1 week and 112 (89.6%) by age 3 months: two infants who died at age 1 and 4 days were identified by "community search."

Initial cardiac diagnosis was confirmed with *both* cardiac catheterization and echocardiography in 71 infants (56.8%). There was an interesting change over time in that by 1985 initial diagnosis was made with *only* echocardiography in 65% of infants, compared with 14% in 1981. During the period of follow-up, infants with TOF underwent a mean of 1.5 cardiac catheterizations, compared with 2.0 for infants with TOF-PA.

Seventy-eight infants (62.4%) underwent open heart repair during the follow-up period. Of these, thirty-one infants (39.7%) had undergone shunt procedures prior to undergoing open repair. The mean weight and age at open repair were 9.3 kg and 20 months, respectively, for patients with TOF, and 13.2 kg and 39 months, respectively, for patients with TOF-PA. Thirty-three infants (26%) underwent shunt procedures only and 22 (18%) did not undergo surgery. Ten (8%) of the unoperated infants had lethal noncardiac anomalies and the remainder were awaiting open repair at last follow-up.

Outcome

The outcomes of the entire group of infants are shown in Fig 1. The overall mortality rate was 28%. Thirteen of the deaths (37%) occurred before age 1 month. Infants dying in the neonatal period had a high rate of pulmonary atresia (eight [62%] of 13 infants), and all but one infant had at least one additional risk factor (trisomy 13 in two infants, severe gastrointestinal or pulmonary anomalies in four infants, and small for gestational age in nine infants). Together, these 13 infants had a total of 47 risk factors (Fig 2). Seven had undergone one or more shunt procedures.

Fifteen of the nonsurviving infants (43%), five of whom had pulmonary atresia, died between age 1 and 12 months; these infants had a total of 40 risk factors. Thirteen infants died following surgery; the deaths of 10 of

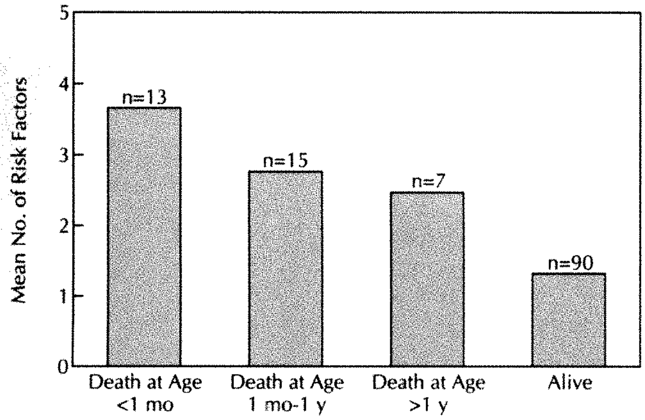

Fig 2.—*Risk factors for mortality in teratology of Fallot. Risk factors include low birth weight, prematurity, pulmonary atresia, associated cardiac anomalies, associated noncardiac anomalies, and age at diagnosis younger than 8 days.*

these infants were attributed to the surgery and the deaths of three to noncardiac anomalies (ie, Di George syndrome, omphalocoele, and adrenogenital syndrome). Two infants died without undergoing surgery; one had pulmonary atresia and extreme prematurity and the other had an acute arrhythmia.

Seven infants died after age 1 year; these infants had a total of 17 risk factors. There were five surgical deaths, four after open repair and one following a shunt procedure. Of the two medical deaths, one infant with pulmonary atresia and prematurity died of hepatopulmonary dysplasia after having undergone a prior shunt procedure, and one infant with trisomy 21 died of leukemia at age 27 months.

Statistical Analysis of Outcome

Results of univariate analyses of potential demographic and clinical risk factors for infant death are shown in Table 1. Sex and race did not influence survival. Low birth weight and prematurity were both risk factors for death (OR [CI] = 2.9 [1.3, 6.8] and 5.9 [2.5, 14.1], respectively). The mean birth weights for surviving and nonsurviving infants were 2964±655 g and 2577±783 g, respectively; the mean gestational ages for surviving and nonsurviving infants were 39±2.7 weeks and 37±3.1 weeks, respectively. Patients with pulmonary atresia (OR [CI] = 4.8 [1.9, 12.1]), additional major cardiac anomalies (OR [CI] = 5.4 [1.9, 15.5]), or major noncardiac anomalies (OR [CI] = 3.4 [1.4, 7.8]) were also at increased risk of dying. Infants diagnosed in the first week of life were significantly more likely to die than were older infants (CI = 4.6 [1.8, 11.5]). The mean age at diagnosis for surviving and nonsurviving infants was 47±74.5 days and 11±28.2 days, respectively. The survival rate for patients with TOF (79%) was nearly double that for patients with TOF-PA (44%). None of the socioeconomic variables tested showed any significant differences between surviving and nonsurviving infants.

Multivariate analysis (stepwise proportional-hazards regression) included the six significant variables in Table 1; all variables except low birth weight remained in the final model (Table 2).

COMMENT

This study evaluated the combined medical and surgical mortality rate for all live-born infants with TOF in a regional birth cohort. The overall mortality rate was 28%.

Table 2.—Risk Factors for Mortality in Tetralogy of Fallot: Results of Cox Proportional-Hazards Regression Analysis

	Parameter Estimates		
Variable	**Coefficient**	**SE**	***P***
Prematurity	1.0305	0.3562	.004
Age at diagnosis >1 wk	0.9666	0.4302	.025
Noncardiac malformation(s)	0.8799	0.3504	.012
Pulmonary atresia	1.122	0.3924	.0042
Associated major cardiac anomalies	1.067	0.3951	.007

Early referral, a major objective of the New England Regional Infant Cardiac Program,[11] is the norm in our region. Almost 90% of infants with TOF were diagnosed by age 12 weeks, reflecting increased awareness by referring physicians of the value of early diagnosis of CVM.[12]

The survival rate in this regional study differed from the outcomes reported in selected cases in surgical series. Walsh et al[3] described 220 infants who underwent primary repair of TOF between 1973 and 1987; there were 17 early (8%) and three late (1%) deaths. Their study included 150 infants (68%) with uncomplicated TOF, 43 (20%) with "complicated" TOF (additional cardiac anomalies excluding absent pulmonary valve) and 25 (11%) with TOF-PA. These excellent results exclude, because of the nature of the study, any risk factors for mortality prior to open repair. In our series, 26 (74%) of 35 deaths occurred without open heart surgery. The surgical mortality rate for uncomplicated TOF was similar between their series and ours (5% and 9%, respectively). Thus, the major outcome discrepancy was attributable to the all-inclusive regional case group in our study and not to differences in surgical techniques.

Prenatal studies of CVM report a lower survival rate at age 1 year than that found in our study of live-born infants. Crawford et al[13] found that only two (33%) of six infants with an in utero diagnosis of TOF were alive after 1 year. This small case series suggests a continuous gradient in outcome severity in TOF; infants presenting in utero have worse outcomes than do live-born infants, who, in turn, have worse outcomes than the selected group represented in surgical series.

The advantage of a population-based study is the ability to obtain outcome data for an unselected cohort of live-born infants and to demonstrate the spectrum of severity involved. In contrast to clinical case series, exclusions were not made due to variations in cardiac anatomy or the presence of major noncardiac defects. Nonetheless, the present study has several limitations. Because only infants diagnosed prior to their first birthday were enrolled in the BWIS, milder cases of TOF are not included. Patients were treated at several pediatric cardiology centers with varying approaches to the timing of surgical repair. Despite its retrospective design, the study was strengthened by obtaining data from multiple sources, including cardiology center reports, medical records, and maternal interviews.

The risk factors for poor outcome in our study included pulmonary atresia, low birth weight, and major additional cardiac and noncardiac anomalies. Race and socioeconomic status were not risk factors. These outcome data reflect the state of management in the early to middle 1980s, a period of increasing movement of cardiac surgery to younger age groups. As further technologic advances are made, it will be interesting to determine whether these risk factors continue to predict outcome in infants with TOF.

The results of this study confirm that TOF has a wide spectrum of severity, ranging from the most severe, such as tetralogy with pulmonary atresia and lethal noncardiac anomalies, to isolated TOF in an otherwise normal infant. The recognition of this severity spectrum and analysis of its clinical and pathogenetic significance is an important part of the etiologic search in regional studies, and can also provide a focus for future developmental and clinical cardiac research.[5]

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Advancing Through the Medical Hierarchy

Innovative and creative leadership on the part of institutions and individuals in positions of authority is needed to confront the stereotypes and limits to women's success that will prevent our field from making the progress that is necessary in the next decade. In order for women to succeed, we must recognize their leadership styles, alter our fixed systems of appointment and promotion, and develop alternative tracks. The future will necessitate that policy be made by all of those affected. It is no longer sufficient to take traditional values and attitudes for granted and expect that they will lead to success in the future.—Carol C. Nadelson, MD, the first woman president of the American Psychiatric Association and professor of psychiatry at Tufts University School of Medicine, Boston, Mass.

Nadelson CC. Advancing through the medical hierarchy. *J Am Med Wom Assoc*. 1991;46:95-99.

Breath-Holding Spells in Childhood

Francis J. DiMario, Jr, MD

• Childhood breath-holding spells are a common and frightening phenomenon occurring in healthy, otherwise normal children. They have been well recognized for several hundred years. There appear to be two clinical forms: the cyanotic type and the pallid type, referring to the color change exhibited by the child during the episode. Prior research concerning the underlying pathophysiologic mechanisms involved in breath-holding spells has implicated an autonomic nervous system dysregulation. Cerebral anoxia is the ultimate factor responsible for the loss of consciousness observed in the severe forms of breath-holding spells. The clinical and epidemiologic aspects of breath-holding spells are herein summarized. The pertinent respiratory and neural physiologic interactions involved are delineated, as well as practical treatment approaches.

(*AJDC*. 1992;146:125-131)

Breath-holding spells (BHS) in childhood are a dramatic and commonly observed clinical phenomenon that attracted much attention during the 1950s and 1960s, becoming the focus of both clinical and epidemiologic study. Investigators have since concentrated more on the pathophysiologic mechanisms causing BHS. The purpose of this review is to summarize and integrate both the clinical perspectives provided in the literature and the pathophysiologic mechanisms involved.

NOMENCLATURE

Breath-holding spells have a number of descriptions based on the specific coloration of the child during the event (cyanotic vs pallid) and specific pathophysiologic mechanism. The most frequently used terms cited in the literature are as follows: cyanotic infantile syncope; anoxic convulsions; pallid infantile syncope; reflex anoxic seizures; nonepileptic vagal attacks; and white reflex syncope.

The distinction, based on a clinically apparent color change, was first put forward by Lombroso and Lerman[1] in the 1960s. This recognition of cyanotic and pallid coloration not only served to separate distinct groups, but also implied an underlying difference in the pathophysiologic characteristics of each type. Breath-holding spells, as referred to in this review, are specified as either cyanotic or pallid. In instances where there is not a clear distinction between cyanosis and pallor, the term *mixed* is used.

HISTORICAL PERSPECTIVES

The earliest written descriptions of breath-holding spells are credited to Nicholas Culpeper, an English herbalist practicing in the early 1600s.[2,3] In his book, he included a section on the cure of infants, in which he described, in running prose, the essential features of a breath-holding spell.[4] Over the succeeding 250 years, several literary authors have commented on this clinical entity, notably Charles Dickens in the chapter entitled "Minders and Reminders" in *Our Mutual Friend*. In-depth historical perspectives on this topic can be found elsewhere.[5]

CLINICAL DESCRIPTION AND NATURAL HISTORY

The term *breath-holding spell* is a misnomer. The name implies a voluntary action resulting in a prolonged inspiration. In actuality these episodes are involuntary and reflexive and occur during active or full expiration. They can be further described as either simple or severe depending on progression from a noiseless expiration, accompanied by color change (simple), to loss of consciousness with change in postural tone (severe).

Figure 1 denotes the typical clinical sequence noted during a breath-holding spell. Generally, there is a provocation that causes anger, fear, reaction to pain, or frustration. Although the provocation is often recognized, the child is frequently found during the clinical spell with no apparent inciting event. Typically, the child begins to cry or display emotional upset, which may be very brief, amounting to one or two whimpers, or a prolonged, gradually intensifying scream. Ultimately, however, the child reaches a point of noiselessness. At this juncture, with the child's mouth wide open in full expiration, the face and trunk change color. After the dramatic noiseless pause, the spell may resolve with a labored inspiration. When the spell resolves before the loss of consciousness, it is termed *simple*. However, if the symptoms continue, a deepening of cyanosis or pallor, or perhaps a mixture of both, will be noted. The child will then appear dazed and ultimately lose consciousness. One then notes a change in postural tone as seen in limpness that quickly progresses to an opisthotonic posture. On occasion, body jerks and urinary incontinence are also observed. The entire event

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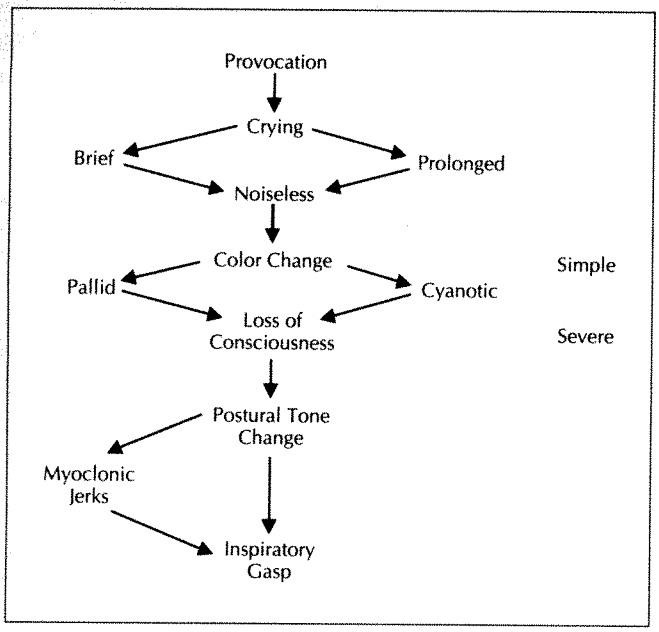

Fig 1.—*The clinical sequence of events defining the typical breath-holding event.*

may terminate with an inspiratory gasp or with the spontaneous resumption of quiet breathing. For several minutes the child may appear drowsy with a dulled sensorium during a motionless hypotonic period. This continues until normal consciousness is gradually recovered. This latter sequence of events distinguishes the "severe" spell from the more common "simple" one.

When confronted with the clinical scenario depicted above, several of the following possible entities should be kept in mind: epileptic seizure; orthostatic syncope; apnea; occult brain-stem tumor; occult brain-stem malformation; familial dysautonomia; Rett syndrome; and prolonged QT syndrome.

Distinguishing BHS from true epileptic seizures is generally the first step in diagnosis. Although epileptic seizures can also cause alterations in body tone, posture, and skin color, the usual sequence involves change in muscular tone and posture before the development of color changes. The most important differentiating feature, however, is the presence of an abnormal rhythmic electroencephalographic (EEG) discharge preceding and ultimately causing the clinical changes noted.

Orthostatic syncope is another possibility to be considered in the differential diagnosis. Syncope may be less predictable in that it is not usually accompanied by crying. The child's medical history would include a more sudden onset with rapid loss of postural muscle tone often accompanied by efforts at protection against falling. This can occur as a result of a rapid change in body position and can be quickly resolved once a horizontal posture is obtained.

Central or obstructive apnea may also cause hypoxia resulting in loss of consciousness and tonic posturing. Apnea is considered to be central when there is no chest wall movement or respiratory effort and no respiratory airflow. An obstructive pattern is confirmed when chest wall movement and respiratory effort are seen, with no respiratory airflow. The clinical sequence and definition of BHS imply that these events occur during wakefulness in healthy, otherwise normal children. The definition would, therefore, not apply to spells occurring during sleep.

Other specific causes of BHS include occult or overt brain-stem lesions that can cause dysfunction within the pontomedullary area of the brain stem. Malformations such as the Arnold-Chiari malformation can be considered in this category.[6] Intrinsic brain-stem infiltrative processes are also a rare possibility.[7] Results of the physical examination and clinical history, as well as the natural course of the illness, are sufficient to distinguish true BHS from those caused by these secondary processes. One must also ascertain that the BHS is not part of a more generalized disorder such as can be seen in autistic girls with Rett syndrome or in familial dysautonomia (Riley-Day syndrome).[8,9] Typical stigmata of Riley-Day syndrome such as corneal ulceration, lack of fungiform papillae on tongue, temperature instability, and diminished cutaneous sensation should help identify this particular disorder. In certain circumstances, gastroesophageal reflux, intracardiac or extracardiac shunting, prolonged QT syndrome, or cardiac arrhythmia also need to be considered.[10]

The natural history of BHS in children is summarized in the Table. These data are derived from a compilation of studies published in the past several decades.[1,11-14] It is difficult to arrive at exact figures for certain variables listed in the figure due to the retrospective nature of the studies and the often incomplete follow-up. Nonetheless, despite differences in data collection, much of the information is complementary and provides a reasonable clinical overview.

Prevalence of Severe BHS

Severe BHS has been reported to occur in approximately 0.1% to 4.6% of healthy children.[1,11] These data vary depending on whether the study was retrospective or prospective.[1,11] The relative prevalence of simple BHS is not as well documented, but has been found in approximately 27% of healthy children.[11]

Clinical Types of BHS

Lobroso and Lerman[1] described the clinical types of BHS seen in 225 severe breath holders. They found that 62% became cyanotic, 19% were considered pallid, and an additional 19% were uncertain or unclassifiable.[1] Laxdal et al[13] published retrospective data on 129 of 150 patients studied, and found that 54% had cyanotic spells, 22% had pallid spells, 12% had both types, and 12% were uncertain or unclassifiable.

Age at Onset of BHS

Breath-holding spells occur most commonly within the first 12 months of life, and virtually all breath holders have had their initial spell by age 2 years. Bridge et al[11] reported that 66 (80%) of 83 patients studied retrospectively had their first spell by age 18 months. Similarly, of a total of 51, 89% of 36 children evaluated prospectively for simple spells had their first spell by age 18 months. Laxdal et al[13] reported that of their 150 patients, 87% experienced their first spell before age 18 months and all had done so by age 42 months. They also noted that seven (5%) of 150 patients had had a spell within the first 2 months of life. The prospective study conducted by Lombroso and Lerman[1] provided data on 193 of a total of 225 patients studied. Sixty-

Clinical Summary of Breath-Holding Spells

Variable	Clinical Findings
Demographics	Cyanotic/pallid
Prevalence, %	
Severe	0.1-4.6
Simple	≥27
Relative frequency, %	
Cyanotic	60
Pallid	20
Mixed	20
Age at onset, mo	
Cyanotic	Neonate to 18
Pallid	12-24
Frequency of spells	Daily to monthly
Remission, %	
At 4 y	50
At 6 y	90
Later syncope	
Cyanotic	Rare
Pallid	17%
Positive family history	20%-30%
Positive reaction to ocular compression, %	
Cyanotic	25
Pallid	61-78

six percent were younger than 12 months, 94% were younger than 24 months, and nearly all were younger than 36 months at onset. They also recognized a small group (15 [8%] of 193 patients) who also had their first spell within the first 2 months of life. Livingston[12] provided his experience on 384 children with BHS and found the mean age at onset to be 12 months, with a range of 3 months to 4 years. However, it is not clear if these data represented simple or severe spells, or a mixture of types.

Frequency of BHS

Frequency varies from many spells in a day to once a year.[1,11-13] The greatest proportion of children with severe BHS, however, experience multiple episodes per week. As many as one third of children experience two to five spells per day. An equal proportion will experience spells once per month or less. The peak frequency is generally seen in the second year of life with a gradual tapering off thereafter.

Termination of BHS

In approximately half of all children with severe spells, the spells terminate by age 4 years. Termination is noted in nearly all children by age 7 to 8 years. These figures are based on retrospective data on 51 of 83 patients originally followed up by Bridge et al[11] for a mean of 9 years, 80 of 83 patients followed up by Lombroso and Lerman[1] for a mean of 12 years, and 106 of 123 patients followed up by Laxdal et al[13] for a mean of 9 years. In a study of 384 patients followed up for a mean of 15 years, Livingston reported that all spells terminated by age 6 years.[12]

Of interest are the families with a history of BHS reported in the pedigrees of affected children. Roughly 20% to 30% of all patients have an identified family member who had suffered from BHS during childhood.[1,13-15] In the only study to use a control group of healthy children, children with epilepsy and mental retardation, and others suffering from non-neurologic chronic diseases, 11% of patients had a family history of BHS.[1] It is not clear, however, from the foregoing material whether these family members suffered from simple or severe spells. In a recent study, I and my colleagues[15] found that in 80% of severe breath holders with a family history of breath holding, syncope, or seizures, the influence was from the maternal side of the pedigree.

Authors have often emphasized parental reports of behavior difficulties in children with BHS. Based on these casual surveys, 18% to 32% of severe breath holders were considered behaviorally difficult compared with 8% of controls.[1,13] Using a standardized assessment tool (Child Behavior Profile and Checklist of Akenbach and Edelbrock), preliminary data from an ongoing prospective study of the behavioral profiles of children with BHS have demonstrated neither significant differences between breath holders and age- or sex-matched controls, nor overt behavioral traits that could distinguish breath holders from controls.[16]

SEQUELAE

The consensus to date is that there is no clear evidence suggesting a high likelihood of lasting sequelae of childhood BHS.[1,11-13] Based on emotional provocation such as the sight of blood or hypodermic needles, syncope has been found to develop in late childhood or adolescence in up to 17% of breath holders followed up on a long-term basis.[1] The later development of seizures has been reported in 0.5% to 4.8% of breath holders, and neurodevelopmental abnormalities in 0% to 3.6%.[1,11,12,17] What has not often been specified is whether the seizures were febrile or nonfebrile in nature. An occasional occurrence of prolonged seizures immediately after a breath-holding event has been reported.[18] Prophylactic anticonvulsant therapy has not always been efficacious in preventing seizures in this circumstance.[18]

Southall et al[19] described three children with complicated perinatal and medical histories who developed "ataxic" cerebral palsy after recurrent episodes of severe "prolonged, expiratory apnea." These children, however, were exceptional and not representative of BHS.[20] A true cause-and-effect relationship between BHS and either epilepsy or neurodevelopmental abnormalities is tenuous at best. Fatalities during BHS have been rare, precipitated by aspiration, and compounded by airway occlusion during forceful cardiopulmonary resuscitation.[21,22] Caution must therefore be exercised when addressing the parental management approach and in prognosticating the outcome of children with BHS who have additional superimposed complicated medical histories.

PATHOPHYSIOLOGIC CHARACTERISTICS

To understand the mechanisms behind BHS in children, we must first familiarize ourselves with the anatomic construct leading to normal respiration. Inevitably it is the interplay among several factors, such as the central control mechanisms of breathing, the autonomic nervous system, and cardiopulmonary mechanics, that results in the maintenance of normal respiration as well as BHS.

In its simplest design, respiration is controlled primarily from the brain stem.[23-25] Inspiratory efferent signals can be influenced by external factors, such as environmental changes in temperature and the gas composition of air. The cerebral cortex also exerts an influence over breathing control, a voluntary one during wakefulness and an involuntary one during sleep. The efferent signals are carried by lower cranial nerves, the phrenic nerve, and the thoracic nerves. These, in turn, serve to open upper airways and bronchi, as well as to innervate the muscles of breathing, ie, the diaphragm and external intercostal musculature. Although we tend to think of expiration as being passive, neural innervation to the internal intercostal muscles as well as the abdominal musculature can be stimulated to provide active expiration.[23-25] However, the system is not open ended. With the help of respiratory tract receptors that initiate the signals carried centrally via cranial nerves in a feedback loop, brain-stem centers are informed of the status of respiration as it occurs.[23-25]

The upper respiratory tract consists of mechanoreceptors located throughout the nasopharynx, larynx, trachea, and bronchi.[23,24] These receptors when stimulated feed back to the brain stem via several cranial nerves (trigeminal, glossopharyngeal, and vagus) to initiate several reflexes including coughing, sneezing, blood pressure increases, and heart rate decreases. The lower respiratory tract consists of several other types of receptors, including airway stretch receptors, which are stimulated by airway distortion such as occurs during overinspiration or excessive expiration. Through the vagus nerve, they in turn inhibit inspiratory efforts and stimulate active expiration.[23,25] Other receptors such as the so-called "J" receptors within the alveolar capillary beds and irritant receptors within the airway walls also feed back via the vagus nerve to mediate fluctuations in blood pressure, heart rate, inspiratory effort, as well as bronchoconstriction and local vasomotor changes.[23]

In a simplistic fashion, the brain stem can be divided into two general respiratory centers. The medulla is the primary control center for rhythmicity or automaticity of inspiration and active expiration.[23] The pons, on the other hand, serves more as a modulator, altering depth and duration of respiration.[23]

Chemosensitive cells on the surface of the medulla respond to changes in the hydrogen ion content within the cerebrospinal fluid. These changes are coincident with fluctuations of P_{CO_2} in the arterial blood supply. Since carbon dioxide (CO_2) readily diffuses into the cerebrospinal fluid, and because it lacks an effective buffering mechanism, the CO_2 undergoes slow hydrolysis to carbonic acid (H_2CO_3), which, in turn, dissociates into hydrogen ion (H^+) and bicarbonate (HCO_3). An accumulation of hydrogen ions stimulates the chemoreceptor cells, resulting in increased inspiratory efforts and a normalization of arterial P_{CO_2}, as well as the maintenance of a constantly normal pH in the cerebrospinal fluid. Long-term elevation of arterial P_{CO_2}, as seen in chronic obstructive pulmonary disease, results in decreased sensitivity of the medullary chemosensory cells. Due to this decreased sensitivity, the peripheral chemosensitive cells located in the carotid and aortic bodies take on this primary stimulatory role. The carotid bodies located in the carotid sinus, and to a lesser extent, the aortic bodies located in the ascending aorta, are preferentially sensitive to P_{O_2} and blood flow. Thus, hypoxia and/or diminished blood flow serve to stimulate their feedback via the glossopharyngeal and vagus nerves, respectively, to influence respirations and heart rate control from the brain stem. In addition, the aortic bodies respond to changes in blood pressure through their barroreceptors, such that both elevations and decreases in blood pressure can affect respiratory efforts.

CLINICAL INVESTIGATIONS

A number of clinical investigations have aimed at determining the precise mechanisms involved in BHS. The initial study by Bridge et al[11] was prompted by parental observations of bradycardia occurring during an episode of breath holding. This so-called vagotonia could be reproduced by applying pressure to the eyeballs.[11] This oculocardiac reflex stimulated by ocular compression results in the transmission of afferent signals to the brain stem via the trigeminal nerve, whereby efferent parasympathetic outflow signals are then transmitted via the vagus nerve to affect the heart rate.[15,26] It was observed in subsequent studies that as a diagnostic maneuver, ocular compression could be used to provoke BHS.[1,26-28]

The method of applying ocular compression has varied somewhat in different studies. Lombroso and Lerman[1] devised a mechanical device termed *ocular tonometer* by which 100 to 200 g of pressure could be applied to each eyeball simultaneously for a full 10-second interval.[1] Most often, however, investigators have used the manual method described by Stephenson[29] of applying the finger pads of the thumbs gently over both closed eyelids.

In a study comparing 92 patients with BHS (44 pallid, 36 cyanotic, and 12 mixed) with a control group of 83 patients, Lombroso and Lerman[1] reported the results obtained using ocular compression. They found that 27 patients (61%) with pallid BHS and nine (25%) with cyanotic BHS experienced an asystole at least 2 seconds in duration.[1] In contrast, a similar response was seen in six controls (7%).[1] Furthermore, no control subject experienced asystole for 4 seconds or longer. Applying ocular compression to 69 patients with BHS, 28 patients with syncope, and 21 patients with uncertain attacks, Stephenson[26] reported asystolic periods of at least 2 seconds in 45 pallid breath holders (78%), 13 children with syncope (46%), four children with cyanotic BHS (36%), and six children with an uncertain attack (29%). In addition, 55% of pallid breath holders and 18% of children with syncope had asystole for 4 seconds or more.[26] Only 6% of the combined cyanotic and miscellaneous groups experienced asystole for 4 seconds or more.[26] Thus, ocular compression resulting in asystole for 2 seconds or more or the precipitation of a clinical attack during ocular compression appears to be more readily inducible in children with pallid BHS than in those with cyanotic episodes (Fig 2). In heterogeneous groups of children undergoing EEG, Gastaut and Gastaut[27] identified 13.5% of 176 patients, I[15] found only 15% of 115 patients, and Haller et al[30] reported 24% of 77 patients with positive responses to ocular compression.

Ocular compression was used by Gastaut and Gastaut[27] to provoke "clinical convulsions" in 176 patients, of whom 24 patients responded by demonstrating a typical breath-holding spell. These 24 children had normal resting EEGs. They studied various physiologic variables during provoked attacks using simultaneous EEG, electrocardiographic, and pneumographic recordings. The authors were able to subdivide this group into three categories based on the proposed physiologic mechanism of their attacks.[27] One group displayed an intense cardiac inhibi-

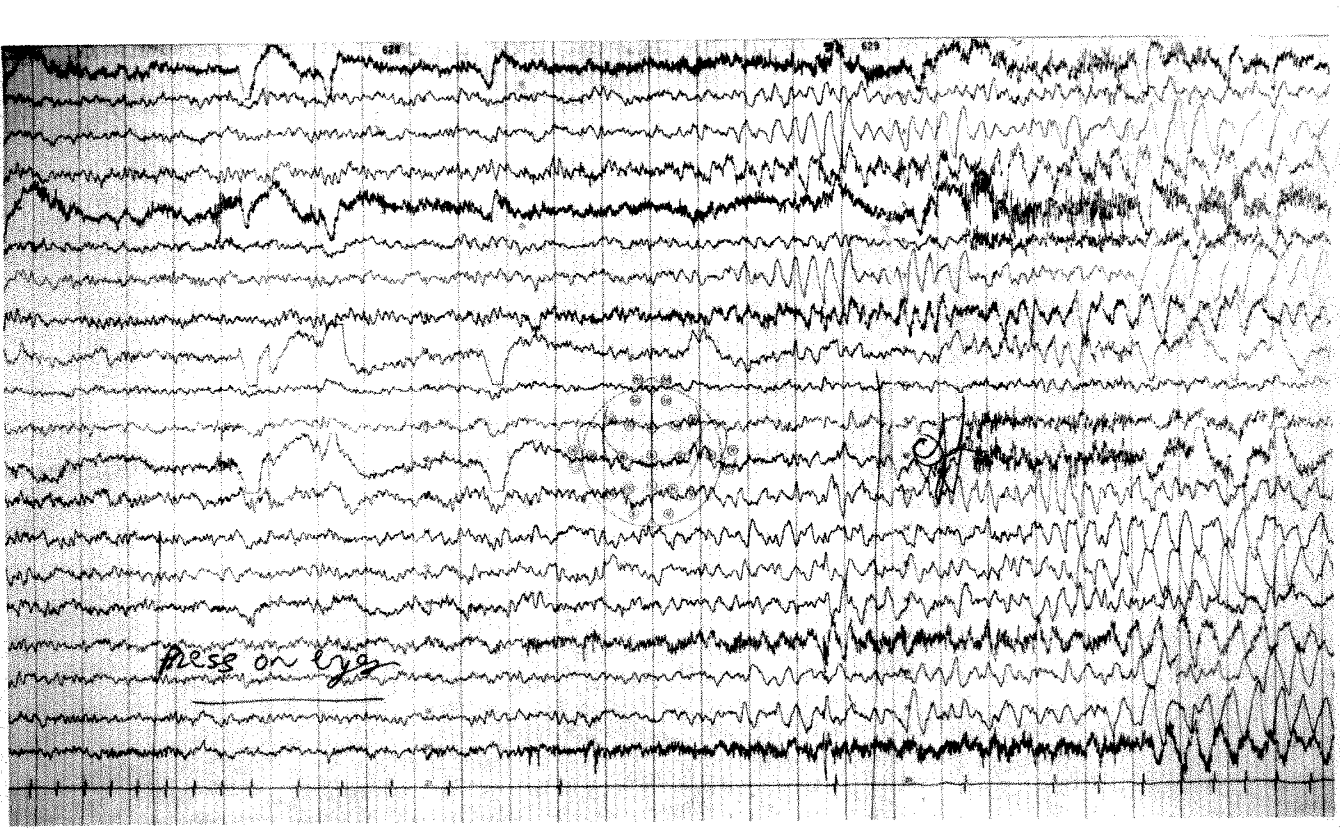

Fig 2.—*An electroencephalographic recording during ocular compression. Note the marked bradycardia (10 beats per minute) in concurrent electrocardiogram at bottom of figure as well as the diffuse slowing and increased amplitude of electrocardiogram during later phase of procedure.*

tion with little respiratory effect and a "pallid" color. The second group displaying intense respiratory inhibition with little cardiac effect was the "cyanotic" group. Last, a third group displaying both intense cardiac and respiratory inhibition was the so-called mixed group. In each circumstance, however, the child exhibited several phases of clinical change that correlated with alterations in physiologic monitoring.[27] Cardiac asystole and/or bradypnea with an attendant color change was accompanied by a burst of slow waves on EEG. This was followed by a stage of deepening color change with loss of consciousness and limpness paralleled by a greater amplitude of continuous slow waves on EEG. Last, a third phase with opisthotonus and generalized muscle jerks was seen in the context of continued slow waves on EEG or electrocerebral silence. Similar EEG correlates of BHS have been reported by a number of authors.[1,14,26-29,31]

Spontaneously occurring episodes in a few children have been studied in the laboratory. Gauk et al[2] were able to monitor several physiologic variables that included intra-arterial blood pressure, respiratory movements, electrocardiography, EEG, and ear oximetry while filming the event. Through their analysis, the following four clinical phases were recognized in sequence: provocation, apnea, rigidity, and stupor.[2] The patient demonstrated a sustained expiration after the first phase, and subsequently developed deepening cyanosis followed by an alteration in muscular tone with concurrent decline in ear oximetry, and a gradual rise in blood pressure without significant alterations in pulse rate. Toward the latter phase, extreme cyanosis and opisthotonus were followed by an inspiratory gasp. The child then lay motionless, drowsy, and breathing on his own. Ear oximetry findings were at their lowest before this inspiratory gasp, and the typical EEG changes as described previously by Gauk et al[2] and Gastaut and Gastaut[27] were again noted. The entire event, through termination with an inspiratory gasp, occurred over approximately a 40-second interval. Extreme cyanosis concurrent with a decrease in resting arterial oxygen saturation from 98% to 40% at nadir led to the suggestion that the clinical and EEG abnormalities were a consequence of cerebral anoxia.[2]

Holowach and Thurston[32] speculated that children who suffered from severe BHS had underlying anemia predisposing to loss of consciousness. They found 23.5% of 102 breath holders had a hemoglobin value less than 80 g/L compared with 6.9% and 2.6% of two control groups.[32] These findings, however, could not be replicated in subsequently published controlled studies by either Laxdal et al[13] or Maulsby and Kellaway,[14] who found no significant differences in hemoglobin concentrations. These discrepancies may relate to demographic sampling biases. In general, anemia cannot contribute significantly to the cause of BHS, but may be an additional influence in individual children. I evaluated a 2-year-old child who had been experiencing simple BHS for 14 months that became frequent and severe when he developed transient childhood erythroblastopenia. His hemoglobin level at that time was 64 g/L. Severe BHS resolved when his hemoglobin level rose to 102 g/L 6 weeks later.

Recent invasive investigations of patients with cyanotic BHS have focused on the expiratory apneic mechanisms involved. Southall et al[19] evaluated nine subjects experiencing repeated prolonged expiratory apneic episodes from infancy (seven patients were younger than 7 weeks and one was an identical twin with a sibling who died of sudden infant death syndrome). Subjects had no response to ocular compression (ie, no asystole for longer than 1.6 seconds or clinical event). Each child was investigated using intra-arterial blood pressure monitoring, transcutaneous Po_2 monitoring, or pulse oximetry, with concurrent electrocardiography, EEG, and respiratory movements.

In addition, several children were also studied with esophageal pressure manometry, expiratory muscle electromyography, chest fluoroscopy, and expiratory airflow measurements. Events were characterized by sustained extreme cyanosis with Po_2 less than 20 mm Hg within 20 seconds of onset, irrespective of whether it was spontaneous or induced by noxious stimuli.[19] Each child had loss of consciousness concurrent with continued expiratory efforts at low lung volumes, without demonstrable intracardiac shunting.[19] An observed rise in arterial blood pressure was without an accompanying change in heart rate. Measurements of abdominal wall movements indicated active expiratory efforts throughout the period of oxygen desaturation. In five of the 10 patients examined, active expiration was against a closed glottis, producing both a reduction in esophageal pressure and a rise in expiratory airway pressure. Two subjects underwent elective tracheostomies to rectify a possible obstructive expiratory component. The breath-holding episodes continued despite tracheostomy in both cases. The proportion of phosphatidylcholine in the tracheal aspirates of five patients was measured and found to be below that of age-matched controls in one subject and low in four others. These findings led the investigators to apply continuous positive airway pressure by way of the tracheostomy tube in the two subjects who had undergone tracheostomies. During treatment with continuous positive airway pressure, the cyanotic episodes stopped, and repeated phosphatidylcholine measurements were found to be normal. The investigators concluded that their patients had normal central and peripheral neurocontrol of respiration; however, due to an excessively compliant rib cage, both lung collapse and stretching of airways stimulated stretch receptor activity. This resulted in an inhibition of inhalation, coupled with active expiration. Forced expiratory effort at low lung volumes resulted in a redistribution of lung gas from the alveoli into the airways with the concurrent rapid development of hypoxemia.[19]

I and my colleagues[15] compared the peripheral autonomic nervous system activity in children with pallid BHS with that in age- and sex-matched controls. Simultaneous measurements of mean arterial pressures, pulse rates, electrocardiographic analyses, and peripheral norepinephrine levels were taken during various changes in position (eg, prone to standing). Compared with controls, breath holders displayed significant ($P<.05$) differences in mean arterial pressures and an unsustained increase in pulse rate during the prone to standing maneuver.[15] In addition, one child with pallid BHS had a plasma norepinephrine level 60% below the mean for both groups. This small study suggested the possibility that an underlying subtle but diffuse autonomic dysregulation was a causative factor of BHS in some children.[15] A more recent prospective study of autonomic function in both cyanotic and pallid breath holders again documented significant differences from controls.[33] These data reaffirm the presence of autonomic dysregulation in these children.

The pathophysiologic characteristics of BHS in childhood appear to be somewhat heterogeneous. There is good evidence to suggest that a central component mediated through the vagus nerve results in a slowed heart rate and probable inhibition of respiratory efforts in some children. In selected cases, particularly infants, lung mechanics may predispose to an inappropriate stimulation of normal pulmonary reflexes resulting in an expiratory apneic episode accompanied by extreme hypoxemia. Last, there is evidence that a more diffuse state of autonomic dysregulation exists in some children with severe BHS. This dysregulation may be under genetic influences helping to explain the later development of reflex syncope as a sequelae to BHS, and the familial tendency toward syncope in members of the extended family.

TREATMENT

The treatment of children with BHS has largely been to provide reassurance to families after a diagnosis has been made. Anecdotal reports of the use of anticonvulsants as prophylaxis against BHS are unsubstantiated. A recent report documented episodes of prolonged seizures occurring in conjunction with BHS, neither of which could be prevented despite adequate anticonvulsant therapy.[18] Thus, providing the parents with an understanding of the mechanisms underlying the genesis of BHS is crucial to its treatment. It is neither feasible nor helpful for parents to attempt to avoid all circumstances that may provoke emotional upset in their child. Even though pain and fear may serve as provocatives, simple frustration and the expression of autonomy are both normal and expected in children of this age group.

However, to the parents' dismay these normal emotional outbursts may go on to provoke a BHS. If parental anxiety leads to continuous attempts at appeasement, the child may soon learn to manipulate the parent with the threat of crying. This does not imply a volitional attempt at breath holding, since these are reflexive and unpredictable. There is, nonetheless, the potential for parents to reinforce behavioral outbursts if appropriate calm firmness is not displayed at times of customary disciplining.[17,26]

If a BHS should occur, placing the child in a lateral, supine position to protect the child's head from inadvertent injury and aspiration are reasonable. It would be prudent to avoid cardiopulmonary resuscitation, especially in circumstances in which the likelihood of aspiration is high (eg, while eating). However, clearing the oral airway when it is occluded is obviously important. Atropine sulfate taken orally three times per day in 0.01-mg doses has been successful in preventing breath-holding spells accompanied by bradycardia or asystole.[1,14,26,34] Transdermal scopolamine, oral theophylline, and pacemakers are among other treatments employed.[35-37]

These therapies should be provided only to carefully selected patients, particularly those experiencing multiple daily events, while employing appropriate precautions (eg, avoidance of excessive environmental heat with anticholinergic therapy). The clinical course must be monitored carefully, especially with those children who do not conform to the "expected" natural history because other diagnoses (eg, epileptic seizures) can always occur concurrently with BHS. Continuous positive airway pressure has been used in neonates.[19] However, the clinical indications and expectations of this mode of treatment have to be further assessed.

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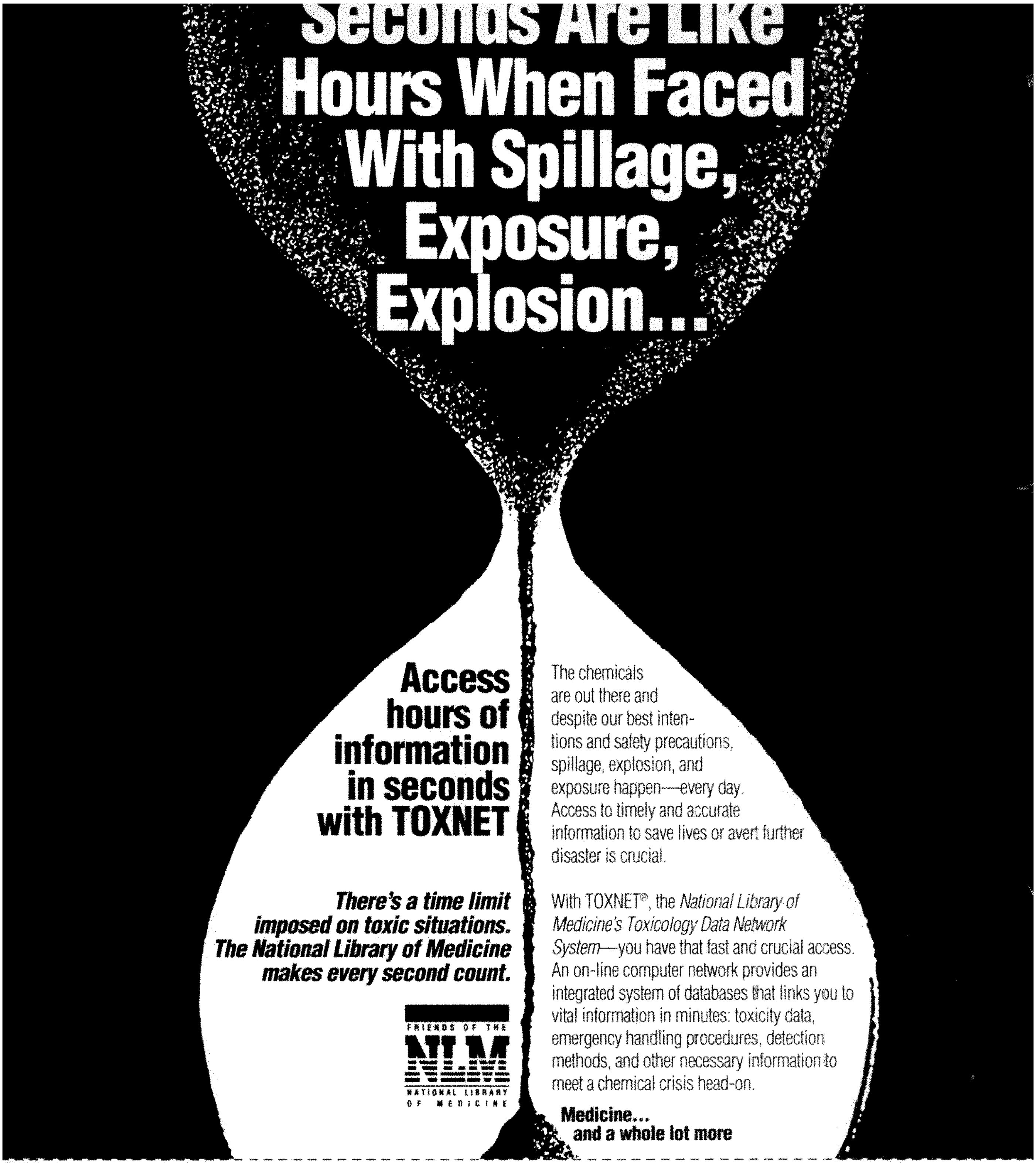
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INDICATIONS AND USAGE

SURVANTA is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

Prevention

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue

To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS

None known.

WARNINGS

SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS

General

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Reproduction studies in animals have not been completed. Mutagenicity studies were negative. Carcinogenicity studies have not been performed with SURVANTA.

ADVERSE REACTIONS

The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, transient bradycardia occurred with 11.9% of *doses*. Oxygen desaturation occurred with 9.8% of *doses*.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

	All Controlled Studies		
Concurrent Event	**SURVANTA (%)**	**Control (%)**	***P*-Value**[a]
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a] *P*-value comparing groups in controlled studies

there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% *v* 30.8%, $P = 0.001$; and 48.8% *v* 34.2%, $P = 0.047$, respectively). The rate in a Treatment IND involving approximately 4400 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 3700 pretreatment and post-treatment serum samples were tested by Western Blot immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardio-respiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal: renal failure, hematuria.

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures.

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia.

Systemic: fever, deterioration.

Follow-Up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies

Six-month adjusted age follow-up evaluations have not been completed. Preliminarily, in 605 (333 treated) of 916 surviving infants, there are trends for decreased cerebral palsy and need for supplemental oxygen in SURVANTA infants. Wheezing at the time of examination tended to be more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Twelve-month follow-up data from the multiple-dose studies have been completed in 328 (171 treated) of 909 surviving infants. To date no significant differences between treatments have been found, although there is a trend toward less wheezing in SURVANTA infants in contrast to the six month results.

OVERDOSAGE

Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED

SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 8 mL of SURVANTA (NDC 0074-1040-08). Each milliliter contains 25 mg of phospholipids (200 mg phospholipids/8 mL) suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

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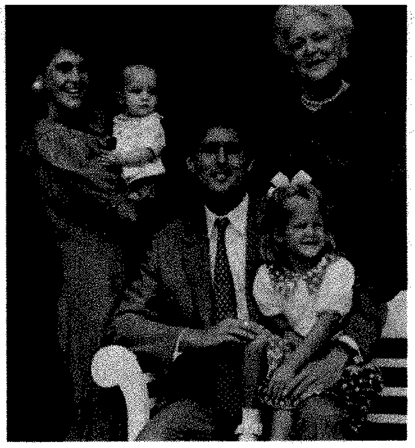

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Applications are available now. Registration is from February 1 through April 30. The application fee established by the ABP for the examination is $1150, but applications postmarked after March 31 must include an additional $200 late fee. Applications postmarked after April 30 cannot be accepted for the 1992 examination. The application fee has not been established by the ABEM, but it will not be less than the ABP fee; it will be announced in the application packet from the ABEM.

Each application will be considered individually and must be acceptable to the Sub-board of Pediatric Emergency Medicine. Please contact the ABP or the ABEM for eligibility requirements. Please direct inquiries to the American Board of Pediatrics, 111 Silver Cedar Ct, Chapel Hill, NC 27514-1651; (919) 929-0461; FAX (919) 929-9255; or American Board of Emergency Medicine, 200 Woodland Pass, Suite D, East Lansing, MI 48823; (517) 332-4800; fax (517) 332-2234.

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Reregistration materials will be mailed to eligible candidates on March 1. The reregistration fee is $1050.

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Immune Response to Hib Conjugate Vaccine

Sir.—The study in the July 1991 issue of *AJDC* on dose-related immunogenicity of one of the conjugate *Haemophilus influenzae* type b (Hib) vaccines could merit from a more detailed analysis of the data.[1] The data presented in several aggregates could be divided into smaller groups for a better appreciation of the effectiveness of the vaccine. The age grouping of the children does not take into account an age-dependent response to conjugate vaccines reported for another vaccine given during the first year of life.[2] Secondly, geometric mean titers do not give a sense of the protection afforded to the vaccinated population.

The pediatric section of the Marshfield (Wis) Clinic performed a similar dose-response study with the conjugate Hib vaccine oligosaccharide-CRM_{197} (HibTITER, Lederle-Praxis Biologicals, Pearl River, NY), in which a cohort of children was vaccinated, starting at age 2 months. Assays for anti–polyributylribitol phosphate (PRP) antibody concentrations were performed by the contractor (Praxis Biologics, Rochester, NY). We present our results as the proportion of vac-

Antibody Responses in Infants Vaccinated With Three Doses of *Haemophilus influenzae* Type B Conjugate Vaccine Oligosaccharide-CRM*

Vaccine Dosage, µg	Post 1	Post 2	Post 3
	% of Subjects With Twofold Increase		
10	1	62.5	94
15	7	67	93
25	28	92	100
	% With Antibody Titer >0.15 mg/L		
10	31	94	100
15	27	87	100
25	54	95	100
	% of Subjects With Antibody Titer >1.0 mg/L		
10	0	44	94
15	0	53	87
25	11	84	97
	Geometric Mean Titers, mg/L		
10	0.14	0.65	11.75
15	0.16	0.93	12.02
25	0.26	3.58	20.84

*Each child was first vaccinated at age 2 months and received a total of three vaccinations. Blood samples were taken 2 months after the first (post 1) and second (post 2) vaccinations and 1 month after the third (post 3). Sixteen children were vaccinated with a 10-µg dose; 15 with a 15-µg dose; and 37 with a 25-µg dose.

cinees who showed any of the following three responses: (1) doubling of concentration from either initial (obtained prior to vaccination) or lowest value; (2) anti-PRP antibody concentration of 0.15 mg/L; or (3) anti-PRP antibody concentration of 1.0 mg/L (Table). For purposes of comparison the geometric mean titers are also included.

It can be seen by the tabulation of data in this manner that geometric mean titers give an imprecise sense of the effectiveness of the vaccine. The use of geometric mean titers does not distinguish the protected children from the unprotected. The usefulness of a vaccine is based on the protection of a proportion of the population, so that arrangements of data such as ours allows us to judge how a vaccine affects the population. While we have yet to determine a more precise measure of protection in relation to anti–PRP antibody concentrations, arrays of data as in the Table will allow comparison of the vaccines.

I suggest that the authors present the data that were obtained for their study in a similar manner, and further, that they segregate the populations vaccinated into age groups of 2 to 6 months, 6 to 12 months, etc, so that an equitable evaluation of their data may be made.

BRADLEY J. SULLIVAN, MD, PHD
Pediatrics, Marshfield Clinic
1000 N Oak Ave
Marshfield, WI 54449

1. Wong VK, Quagliata R, Adler R, Kim KW. Dose-related immunogenicity of *Haemophilus influenzae* type b capsular polysaccharide–*Neisseria meningitidis* outer membrane protein conjugate vaccine. *AJDC.* 1991;145:742-745.

2. Madore DC, Johnson CL, Phipps DC, et al. Safety and immunologic response to *Haemophilus influenzae* type b oligosaccharide-CRM$_{197}$ conjugate vaccine in 1- to 6-month-old infants. *Pediatrics.* 1990;85:331-337.

In Reply.—Dr Sullivan raises two important considerations when evaluating vaccines in children, immunogenicity and efficacy, ie, protection against invasive *Haemophilus influenzae* type b disease. Our data demonstrating an inverse relationship of immunogenicity and *Haemophilus influenzae* type b capsular polysaccharide–*Neisseria meningitidis* group B outer membrane protein conjugate vaccine (PRP-NOMP) dosage after a second dose of PRP-NOMP cannot directly address the issue of efficacy. We agree that if we were to assume that children achieving anti-PRP antibody levels greater than 1.0 mg/L were protected against *H influenzae* type b disease, our finding of anti-PRP geometric mean titers of 7.3 mg/L after the second dose of PRP-NOMP in the 30-µg PRP dosage may not be of clinical significance (as stated in our article) because almost all the children achieved anti-PRP antibody levels greater than 1.0 mg/L. The suggestion that "protection in relation to anti-PRP antibody concentration" can be better assessed by comparing age with percentage of children with twofold increase or with levels of 0.15 mg/L or 1.0 mg/L than with anti-PRP antibody geometric mean titers without appropriate efficacy data has not been established. In comparing immunogenicity data of various *H influenzae* type b vaccines, it should be noted that

Table 1.—Percentage of Children With Anti–Polyributylribitol Phosphate (PRP) Antibody Level Greater Than or Equal to 1.0 mg/L Among 2- to 18-Month-Old Children Who Received 7.5, 15, or 30 µg of PRP

	% of Children by Age Group, mo					
	2-6 (n=27)		7-12 (n=26)		13-18 (n=13)	
Vaccine Dosage, µg	Vaccination 1	Vaccination 2	Vaccination 1	Vaccination 2	Vaccination 1	Vaccination 2
7.5	100	100	88	100	83	100
15	78	100	89	89	67	100
30	89	89	67	89	100	100

Table 2.—Comparison of Geometric Mean Anti-PRP Antibody Concentrations in 2- to 18-Month-Old Children*

		Geometric Mean Anti-PRP Antibody Concentration, mg/L (95% CI)	
Age, mo	No. of Children	Vaccination 1	Vaccination 2
2-6	27	4.1 (2.2-7.4)	6.8 (3.8-11.9)
7-12	26	2.2 (1.2-3.9)	5.3 (3.0-9.5)
13-18	13	4.6 (2.3-9.2)	9.4 (4.2-20.9)

*PRP indicates polyributylribitol phosphate; CI, confidence interval.

there are several compounding factors affecting immunologic responsiveness to the vaccines, eg, laboratory assay for anti-PRP antibody quantitation, study designs, and statistical analysis.

We would like to assure Dr Sullivan, however, that we did evaluate the immunogenicity of the PRP-NOMP vaccine by "segregation" into smaller groups (ie, age groups of 2 to 6, 7 to 12, and 13 to 18 months) and by whether anti-PRP antibody levels doubled or were greater than or equal to 0.15 mg/L or 1.0 mg/L after immunization. We failed to note any significant differences based on age at administration of vaccination if the children were younger than 18 months at time of immunization (comparison of percentage of children with anti-PRP antibody levels greater than or equal to 1.0 mg/L and geometric mean titers by age groups is presented in Tables 1 and 2).

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Intravenous Immune Globulin and Aseptic Meningitis

Sir.—We report the case of a patient with aseptic meningitis that was probably caused by the administration of intravenous immune globulin (IVIG).

Patient Report.—A 9-year-old boy was admitted to the hospital 1 day after the development of epistaxis and hematemesis. Results of physical examination were unremarkable except for petechiae on the palate. A complete blood cell count revealed a hemoglobin level of 99 g/L and a white blood cell count of 7.2×10^9/L, with 0.24 segmented neutrophils, 0.68 lymphocytes, 0.05 monocytes, and 0.03 eosinophils. His platelet count was 16×10^9/L, and a peripheral blood smear showed a decreased number of platelets and giant platelets. A clinical diagnosis of immune thrombocytopenic purpura was made. Intravenous immune globulin (400 mg/kg of body weight; Sandoglobulin IV, Sandoz Pharmaceuticals, East Hanover, NJ) was infused over 4 hours daily for 2 days. His platelet count increased to 69×10^9/L within 48 hours of starting infusion. Approximately 12 hours after completion of the second dose of IVIG, the patient complained of headache. He also developed fever and vomited once. Results of neurologic examination revealed the patient to be lethargic, with normal fundi but a stiff neck. A computed tomogram of the head was normal. Lumbar puncture revealed cloudy cerebrospinal fluid. Analysis of the cerebrospinal fluid revealed the following values: white blood cell count, 2.5×10^9/L (0.98 segmented neutrophils and 0.02 lymphocytes); protein, 0.60 g/L; and glucose, 4.1 mmol/L. A gram stain of the sediment was negative for bacteria, and viral (enteroviruses and herpes simplex) and bacterial cultures of cerebrospinal fluid were negative. Results of tests of renal and hepatic function were normal. Results of tests to detect antinuclear antibodies and anti-DNA were negative, and his C3 serum complement was normal. Administration of IVIG was discontinued after the second dose, and the patient began a short course of prednisone therapy (3 mg/kg of body weight per day for 4 days).

The patient became completely asymptomatic within 24 to 48 hours of the onset of neurologic symptoms. His platelet count was normal 4 days after hospitalization, and he was well at this writing.

Comment.—The clinical presentation and course of aseptic meningitis in this patient are similar to those in previously described patients.[1-3] Six episodes of aseptic meningitis, two in each of three patients, have been reported (Table). In four of these episodes, including that of our patient, headache, fever, and neck stiffness developed within 48 hours of administration of IVIG. In one patient, both episodes occurred 7 days after IVIG therapy, despite using a different IVIG preparation the second time. The white blood cell count in cerebrospinal fluid ranged from 0.18×10^9/L to 2.45×10^9/L, with greater than 0.90 neutrophils, an unusual finding in aseptic meningitis. All patients had rapid and complete recoveries.

The development of aseptic meningitis after IVIG administration in several patients with similar clinical courses adds supportive evidence to a causal relationship between the two; the mechanism of such a relationship is unknown. While headache, fever, and vomiting are reported to be frequent side effects of therapy with IVIG, what proportion of patients have laboratory evidence of aseptic meningitis is unknown. It is also of interest that all reported cases of aseptic meningitis occurred in patients with immune thrombocytopenic purpura and after improvement in platelet count.

Physicians should be aware that this clinical syndrome exists, that results of analysis of cerebrospinal fluid may be significantly abnormal in these patients, and that the outcomes reported to date have, to our knowledge, been uniformly good.

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Intubation of Newborns

Sir.—Newborns admitted to the neonatal intensive care unit (NICU) frequently require laryngoscopy and endotracheal intubation. These procedures may be associated with detrimental physiologic alterations, including bradycardia, hypoxemia, systemic hypertension, and increased intracranial pressure (ICP).[1,2] In addition, they are uncomfortable and at times painful procedures with the potential for traumatic injury to the upper airway.

It is standard practice in pediatric and adult intensive care units to premedicate patients undergoing nonemergency endotracheal intubation. Various medications are used, including atropine sulfate combined with a sedative and, sometimes, a muscle relaxant. The use of these medications provides more favorable conditions for intubation and ensures patient comfort. Studies of neonates have shown that some of the adverse physiologic consequences of laryngoscopy and intubation can be attenuated with the use of these agents.[2-4]

In our NICU, we routinely use atropine and a sedative, which is usually a short-acting barbiturate or a narcotic, before nonemergency intubations. A muscle relaxant is also frequently used. During intubation, the infant is continuously monitored to detect bradycardia and hypoxemia with electrocardiography and pulse oximetry. We were interested in finding out if NICUs across the country followed a similar practice.

Methods.—A survey was conducted of 101 NICUs with accredited fellowships in neonatal-perinatal medicine to determine the prevailing method of intubating newborns. Specifically addressed was whether atropine, sedatives, and depolarizing or nondepolarizing muscle relaxants were used before nonemergency intubations. This survey excluded intubations occurring in the delivery room. The sample represented 37 states and the District of Columbia; 74 out of 101 centers responded.

Results.—All respondents denied routine use of atropine before intubations, although one respondent admitted occasional use. When asked why atropine was not used (respondents were given more than one choice), 82% indicated that its use was unnecessary, and 22% considered atropine not to be beneficial. Fifteen percent stated that the use of atropine in this setting was contraindicated because it may dry secretions and mask the clinical sign of bradycardia that results from hypoxemia during intubation. Four percent were reluctant to use atropine because its efficacy as a premedication for intubation is unproven.

Eighty-four percent of respondents never or only rarely use sedatives, 13% sometimes use them, and only 3% routinely use them. Of those who use sedatives, 76% limit their use to full-term newborns who are "difficult" to intubate. Narcotics are the agents of choice.

In 97% of institutions, succinylcholine chloride and a nondepolarizing muscle relaxant (ie, pancuronium bromide) are never or only rarely used to facilitate intubation. Eighty-eight percent of institutions restrict use of these drugs to full-term newborns who are "difficult" to intubate. Data are summarized in the Table.

Comment.—Intubation performed while the patient is awake is the preferred method of intubation in most neonatal units in academic centers across the country. In an emergency, there is little doubt that this is the quickest way to secure the airway; there is no time to medicate the patient. In our neonatal unit, approximately 10% of intubations fit into this category. Most intubations are more controlled; that is, oxygenation is easily maintained with bag-mask ventilation. For these intubations, the use of medications might prove advantageous. There are only a few studies that have examined this issue.

Frieson et al[2] compared two groups of six premature newborns undergoing endotracheal intubation. Group 1 received atropine alone, while group 2 received atropine, a nondepolarizing muscle relaxant, and an anesthetic, which was either inhalational or a narcotic. Patients in group 1 experienced a mean increase in anterior fontanelle pressure of 197% lasting a mean of 28 seconds, while patients in group 2 experienced no significant change in anterior fontanelle pressure. Patients in group 1 also had a greater increase in systolic blood pressure, and the mean length of laryngoscopy was slightly greater than that of patients in group 2.

Kelly and Finer[3] examined three groups of neonates, each consisting of 10 subjects undergoing endotracheal intubation. Group 1 served as controls and were not premedicated, while group 2 received atropine alone, and group 3, atropine and pancuronium. When compared with controls, significantly fewer patients in group 2 had bradycardia, but changes in blood pressure, oxygenation, and ICP were comparable. Significantly fewer neonates in group 3 experienced bradycardia compared with controls, and group 3 patients had the lowest elevation of ICP of all groups. The hypertensive response to intubation was not obviated with pretreatment with atropine and pancuronium.

Barrington et al[4] compared a group of neonates receiving atropine alone with a group receiving atropine and succinylcholine before laryngoscopy and intubation. They found that the decrease in transcutaneous P_{O_2} levels and the increase in ICP associated with intubation were significantly less in the group treated with succinylcholine and that the time necessary to complete intubation was significantly shorter in this group. Again, the hypertensive response to intubation was not altered with pretreatment with atropine alone or atropine and succinylcholine.

Several conclusions can be made from these studies: premedication with atropine prevents the vagal bradycardia associated with endotracheal intubation; the addition of a

Frequency of Use of Sedatives and Muscle Relaxants as Premedications in Newborns Undergoing Endotracheal Intubation*

	Never	Rarely	Sometimes	Routinely
Sedatives	57	27	13	3
Succinylcholine chloride	77	20	3	0
Nondepolarizing muscle relaxant	76	20	4	0

*Data (percentages) are from 74 neonatal intensive care units.

muscle relaxant lowers the increase in ICP, but does not affect the increase in blood pressure; the combination of a sedative or analgesic agent with atropine and a muscle relaxant maintains blood pressure, heart rate, ICP, and oxygenation levels closest to baseline.

Aside from the clinical benefits described in these studies, there are other important considerations. Patient comfort and pain control have become increasingly important issues in the intensive care unit, especially in neonates. It is well known that neonates have intact neural pathways for pain and that nociceptive input leads to the same hormonal, metabolic, and cardiorespiratory changes observed in adults.[5] In older patients, appropriate analgesic agents and sedatives are administered before subjecting patients to surgery or invasive procedures. This practice should also be followed in neonates whenever possible. Moreover, iatrogenic injury to the airway is likely to be reduced by minimizing patients' struggling and decreasing the time spent performing laryngoscopy.

These agents should not be used by inexperienced clinicians or in infants with unstable airways in whom bag-mask ventilation is difficult. They should only be used when adequate monitoring, including pulse oximetry, is available. However, for personnel who are skilled in and comfortable with managing conditions affecting the neonatal airway, we suggest that premedications may be a valuable adjunct to intubation. This viewpoint is shared by the limited number of investigators who have explored this issue. We are surprised that most NICUs in training institutions across the country still perform intubations while patients are awake. We believe that the use of medications to facilitate intubation in newborns warrants further investigation and are initiating controlled studies to examine this issue.

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Pubic Hair in Infancy

Sir.—Pubic hair developing before age 1 year is rare and to our knowledge, development of pubic hair before age 6 months has not been previously reported.[1,2] We describe our experience with three infant girls who developed pubic hair within the first year of life.

Patient Reports.—PATIENT 1.—A white infant girl was born with two or three strands of pubic hair that were first noticed by nursing personnel and later confirmed by the mother. The full-term infant weighed 3220 g at birth and was the product of an uncomplicated pregnancy. Her mother denied virilization or hirsutism and use of any medications during this or prior pregnancies. Pubic hair increased in amount slowly during the first 12 months, resulting in a referral for an endocrinologic evaluation at age 13 months. Her history was unremarkable, with normal growth and development and no history of ingestions, vomiting, vaginal bleeding, or body odor. Parents were nonconsanguineous and of normal stature, and the mother had menarche at age 13½ years.

At age 13 months, the infant had Tanner III pubic hair that was pigmented and curly and confined primarily to both labia. The clitoris was not enlarged. On rectal examination, a small prepubertal sized uterus was palpable. There was no breast development, acne, axillary hair, posterior labial fusion, or hyperpigmentation.

PATIENT 2.—A white infant girl developed pubic hair at age 8 months. She was the product of a full-term, uncomplicated pregnancy. The mother denied virilization or hirsutism and the use of any medications during the pregnancy. The infant's medical history was unremarkable, including normal growth and development. There was no history of vaginal bleeding, vomiting, body odor, or known ingestions. The parents were nonconsanguineous. The mother developed pubic and axillary hair at approximately age 8 years and had menarche at age 10 years.

At age 11 months, the infant had 10 to 15 pubic hairs on each labia, lightly pigmented and straight (Tanner II). Her clitoris was not enlarged and she had no acne, axillary hair, posterior labial fusion, hyperpigmentation, or breast development.

PATIENT 3.—A white infant girl was referred to our institution at age 6 months because of pubic hair present since age 3 months. She was delivered via cesarean section after a full-term pregnancy. Her mother denied virilization or hirsutism and the use of any medications during the pregnancy. The mother reported becoming increasingly hirsute after the pregnancy, although she reported continued regular menstrual cycles. Examination of the mother revealed pubic hair extending to the umbilicus, but no other evidence of excess body hair or virilization. The infant's medical history was unremarkable, indicating normal growth and development. She had no history of vaginal bleeding, vomiting, or body odor. The parents were nonconsanguineous, and reported no abnormalities of their own pubertal development.

On physical examination, the infant showed no signs of acne, axillary hair, hyperpigmentation, or breast development. Examination of the external genitalia revealed generous dark pubic hair on both labia (Tanner III). The clitoris was not enlarged, and there was no evidence of posterior labial fusion.

All three infants remained healthy during 12 to 30 months of observation. In all three, pubic hair progressed slowly, and no other signs of virilization developed.

All three infants underwent corticotropin-stimulation testing (0.125 mg of cosyntropin administered to patient 3, and 0.25 mg of cosyntropin administered to patients 1 and 2) via intravenous bolus infusion. Levels of Δ^5-17-hydroxypregnenolone (Δ^5-17P), 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone (DHEA), Δ^4-androstenedione (Δ^4-A), and testosterone were measured 60 minutes after administration of corticotropin. All assays were performed by Endocrine Sciences, Tarzana, Calif.

Results of the corticotropin-stimulation tests are summarized in the Table. All three patients had slightly exaggerated Δ^5-17P responses to corticotropin and

Patient Data and Test Values for Three Infant Girls With Premature Development of Pubic Hair*

	Patient 1	Patient 2	Patient 3
Age at which pubic hair first noticed	Birth	8 mo	3 mo
Age at examination	13 mo	11 mo	6 mo
Height, cm (percentile for age)	76.8 (75)	76.2 (80)	66.7 (60)
Weight, kg (percentile for age)	9.5 (50)	10.2 (80)	7.6 (60)
Bone age	18 mo	. . .	. . .
Pubic hair, Tanner stage	III	II	III

	Test Values 60 Minutes After Administration of Corticotropin			
	Patient 1	Patient 2	Patient 3	Normal Values
Δ^5-17P, ng/dL	359	409	1298	229 ± 39†
17-OHP, ng/dL	105	103	112	99 ± 13†
DHEA, nmol/L	3.5	13.2	8.4	9.5 ± 0.9†
Δ^4-A, nmol/L	1.1	2.4	1.7	5.3 ± 1.5†
Testosterone, nmol/L	0.3	0.2	0.2	<2.8‡
Δ^5-17P:17-OHP ratio	3.4	4.0	11.6	1.92 ± 0.27†
DHEA:Δ^4-A ratio	3.2	5.5	4.9	<7.0‡

*Ellipses indicate data not available; Δ^5-17P, Δ^5-17-hydroxypregnenolone; 17-OHP, 17-hydroxyprogesterone; DHEA, dehydroepiandrosterone; and Δ^4-A, Δ^4-androstenedione.

†Mean values ± SD for prepubertal children.[3,4]

‡Normal values for healthy adult women.[5] Normal prepubertal responses are undefined.

variably increased ratios of Δ^5-17P to 17-OHP. Patient 3 demonstrated a Δ^5-17P to 17-OHP ratio much higher than the upper limit of normal, even for normal adult women,[5] possibly indicative of a nonclassic 3β-hydroxy-Δ^5-steroid dehydrogenase (3β-H-Δ^5-SD) deficiency.[5] Unstimulated levels of DHEA, Δ^4-A, and testosterone in the mother of patient 3 were all in the normal range for age and sex (2.6, 5.0, and 0.9 nmol/L, respectively).

Comment.—Premature pubarche, the onset of pubic hair before age 8 years in girls and age 9 years in boys, was first described by Silverman et al[1] in 1952. They described 29 children with isolated sexual hair developing before age 8 years. They concluded that premature pubarche was a benign process related to either an increased sensitivity of hair follicles to normal concentrations of androgens or increased adrenal androgen secretions. Various origins have since been proposed. Some investigators have found enzymatic defects,[6-8] most notably, deficiencies in nonclassic 3β-H-Δ^5-SD, 11β-hydroxylase, and 21-hydroxylase, and others have simply noted increased levels of androgens in the blood.[3,9,10] Some studies have suggested ethnic predilections for premature adrenarche and the various nonclassic forms of congenital adrenal hyperplasia.[2]

Our report is of particular interest because all three subjects developed pubic hair in the first year of life. Two of the 29 children described in the original report of premature pubarche by Silverman et al[1] developed pubic hair in the first year of life. More recently, Oberfield et al[2] reported observations from a study of 34 black and Hispanic children with premature adrenarche, including three children between ages 8 and 12 months. To our knowledge, the development of pubic hair in the first 6 months of life has not been previously reported.

Results of corticotropin testing of the infants in our report suggested that one infant may have had a nonclassic 3β-H-Δ^5-SD deficiency. This conclusion is conjectural, particularly considering the paucity of normative data pertaining to adrenal steroid responses to corticotropin in infancy. Oberfield et al[2] reported that one of the three affected infants younger than age 1 year in their study was initially believed to have had a 3β-H-Δ^5-SD deficiency, based on results of corticotropin-stimulation testing, but had a normal response when the test was repeated. This suggests either a lack of intrasubject reproducibility of results of the corticotropin-stimulation test or some maturational variability in Δ^5-17P and Δ^4-A hormonal responses to corticotropin. The abnormally high Δ^5-17P value in our youngest patient adds supportive evidence to the latter possibility and may reflect a normal delay in fetal adrenal-zone involution.

All infants in our report were white and otherwise in good health. They lived in separate geographic areas within one state, had no common ancestry or ethnicity, and had no known exposures to gonadal steroids.[11] The mother of one affected infant reported a slight increase in body hair after the pregnancy, although she had no other signs of virilization, including temporal hair loss, facial hair, deepening of the voice, or clitoral enlargement. Rarely, as is noted by Jean D. Wilson, MD (oral communication, July 1989), a maternal virilizing tumor, such as luteoma of pregnancy, may be associated with pubic hair evident from birth, but clitoral enlargement also is usually present[12] and both tend to regress rapidly after delivery. Thus, the history of steady progression of pubic hair in the affected infants described herein is strong evidence against a maternal tumor.

Because pubic hair typically develops later than clitoral enlargement in infant girls exposed to excess androgens,[13] we suspect that isolated pubic hair in these and certain other children with premature pubarche may reflect an increased sensitivity of hair follicles to normal androgen levels. However, the presentation of all three cases from a relatively small geographic area during a single 12-month period suggests the possibility of some as yet unidentified common genetic or environmental link.

These cases underscore the paucity of data pertaining to very early pubic hair development. Although current evidence suggests that premature pubarche in infancy is benign, close observation and careful supervision of affected infants seems logical and prudent until more clinical data have been accumulated.

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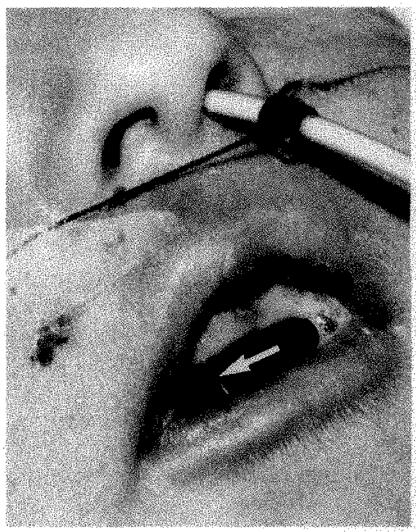
Neonatal Presentation of Prader-Willi Syndrome

Sir.—The article by Aughton and Cassidy[1] in the November 1990 issue of *AJDC* added useful information on the characteristics of neonates with Prader-Willi syndrome (PWS). Unlike Aughton and Cassidy, who did not examine the patients in the neonatal period (or so it appears from their article) and whose study was retrospectively derived from medical records, I have diagnosed a substantial number of newborns with PWS before and after my study in 1980.[2] I conclude that if pediatricians, neonatologists, pediatric neurologists, or geneticists consistently notice an abnormal finding, this is evidence of its importance (for example, the consistently abnormal cry).[1] However, failure to observe what I regard as characteristic features may reflect inadequate examination technique, limited experience, or difficulty in recognizing novel or unexpected phenomena.



"String sign" of sticky saliva (arrow) in a 2-week-old girl with clinical Prader-Willi syndrome.

I have previously suggested[2] that the typical neurologic features of neonatal PWS, and more recent cases have not altered such conclusions. These newborns do *not* have general "hypotonia"; they have striking nuchal hypotonia (similar to but not as severe as in neonatal very long-chain fatty acid oxidation–defective peroxisomopathies[3] or severe glutaric aciduria type 2) but normotonic or dystonic limbs. Most neonatal specialists have difficulty in eliciting the newborn's deep tendon reflexes. So do I, but with patience and attention to technique, normal or brisk responses can be achieved in all cases. Some aspects of the neurologic examination require special skills and proper tools (I have seen a hard triangular-ended rubber tendon hammer used on infants in North America): none would suggest that because most pediatricians cannot play Dvorak's concerto that the cello is a tuneless instrument.

Again, although Aughton and Cassidy[1] correctly note that I said that "the penis was small but could never be described as tiny,"[2] nevertheless, they accepted as valid the lack of appreciation of smallness by the examiners of their cases. I based my comment on measurements of penile length and the available literature on normal values as reported previously.[4] Surely it is recognized that dysmorphism requires measurement: a 2.5-cm penis may appear normal.

A characteristic of neonatal PWS (noticed in all patients whom I have examined) is "sticky" saliva, a feature not mentioned by Aughton and Cassidy.[1] This sign is well described in children and adults with PWS, but has not been so far as I know previously emphasized in the newborn. The saliva has the appearance of being viscous or having high surface tension so that when the newborn's mouth is opened ropes of saliva are seen bridging the oral orifice, the neonatal "string sign" (Figure). Quantitative studies of the physical characteristics of neonatal saliva are in order in PWS, in other conditions with feeding difficulty, and in normal newborns.

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In Reply.—We thank Dr Stephenson for his insightful comments. His observations of sticky saliva in infants with PWS are particularly fascinating and merit especial attention in the prospective studies for which he calls and for which retrospective studies such as ours hope to provide foundation. Similarly, his fine observations of the subtleties of hypotonia in infants with PWS are also most interesting.

"Absence of proof is not proof of absence," and the failure of the majority of examiners to demonstrate brisk deep tendon reflexes in infants with PWS does not absolutely imply that such brisk reflexes can never be elicited. However, we must question the value of a diagnostic sign that is likely to be elicited only by clinical virtuosi; while the brisk tendon reflex may be an excellent diagnostic sign in Dr Stephenson's hands, we think that it is probably of limited value to the average practitioner.

Regarding the penile size of male infants with PWS, we fully agree that "a 2.5-cm penis may appear normal"; this is why we chose the descriptive phrase, "*apparently* normal phallus," so as to reflect our appreciation that final resolution of the commonness (or lack thereof) of true microphallus among these infants will require prospective ascertainment of cases, measurement of stretched penile lengths, and comparison with matched controls. While "microphallus" may simply *denote* a phallus whose length is less than 2 SDs below the mean, it may *connote* something more, namely, a *strikingly* small phallus or a phallus whose smallness is evident on inspection. The results of our study strongly suggest that the practitioner who believes that all male infants with PWS have penises that are small on *inspection* is likely to miss the diagnosis.

Finally, to clarify, two of the five patients in our study who were examined in the neonatal period by a clinical geneticist were examined as neonates by one of us (S.B.C.), and another of the five was examined by both of us. In addition, each of us has examined infants with PWS who were not included in our study, and, of course, one or both of us eventually examined, at some time, all patients included in the study.

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There Are No Children Here

When a journalist told the mother of two boys, ages seven and ten, living in the Chicago housing project that he wanted to write a book about their lives, the mother responded, "But you know, there are no children here. They've seen too much to be children."—Alex Kotlowitz

Kotlowitz A. *There Are No Children Here: The Story of Two Boys Growing Up In the Other America.* New York, NY: Doubleday & Co Inc; 1991:X.

Prescribe

℞ **Pedia-Profen®**

Ibuprofen Suspension

100 mg/5 ml

Provides 6 to 8 hours of fever relief[1]

- **Effective fever relief is achieved with 2 levels of dosing:**
  - — 5 mg/kg for fevers under 102.5°F
  - — 10 mg/kg for fevers 102.5°F and higher
- **Pleasant tasting and easy to swallow**

℞
Pedia-Profen Suspension
100 mg/5ml 4oz.
Sig: 1 tsp q 6-8 hrs.
for fever

Please see brief summary of Prescribing Information on the next page.

McNEIL

McNeil Consumer Products Company
Division of McNeil-PPC, Inc.
Fort Washington, PA 19034 U.S.A.

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Reference: 1. Walson PD et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17

information in **Pedia-Profen** labeling.

INDICATIONS AND USAGE: Pedia-Profen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: Pedia-Profen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **Pedia-Profen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Pedia-Profen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **Pedia-Profen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **Pedia-Profen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **Pedia-Profen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Meaningful (3 times the upper limit of normal), elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with **Pedia-Profen**. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), **Pedia-Profen** should be discontinued.

Safety and efficacy of **Pedia-Profen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **Pedia-Profen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: Pedia-Profen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—orange, berry-vanilla flavored

Bottles of 4 oz (120 ml) .... NDC 0045-0469-04
Bottles of 16 oz (480 ml) .... NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature.

Caution: Federal law prohibits dispensing without prescription.

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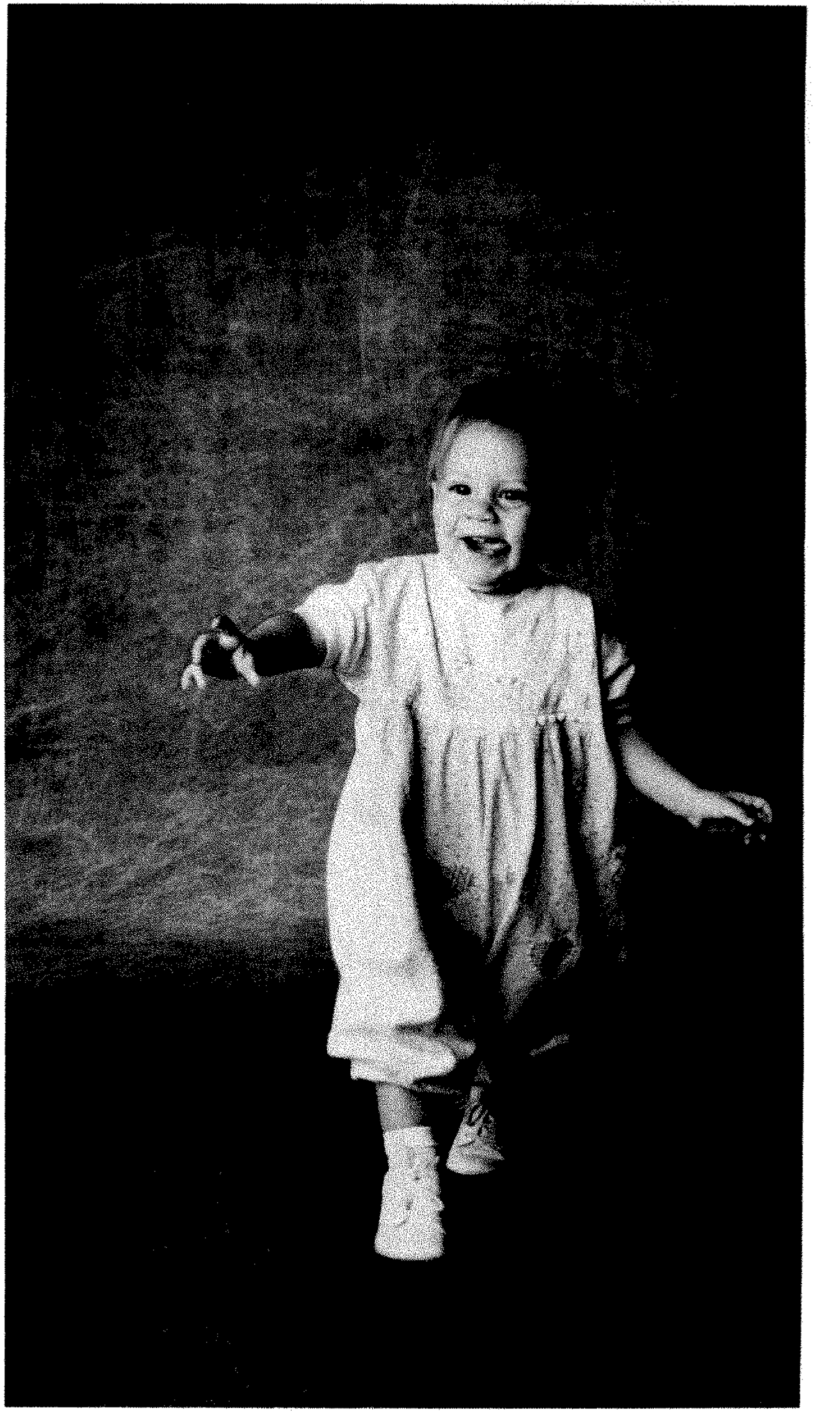

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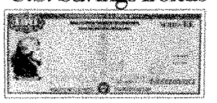

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Poliovirus Vaccine Live Oral Trivalent
I didn't.
Victory
ST. M
24

Jackie, Gina, and Krista DiLorenzo are all superior athletes. Jackie is a world champion table tennis player. Her daughters excel in track and basketball. Unfortunately, Jackie must perform her sport in a wheelchair. Because, unlike Gina and Krista, Jackie was born too soon for ORIMUNE. Jackie is thankful her daughters were protected.

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Protecting Families Through Immunization®
Please see adjacent page for brief summary of Prescribing Information.

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Lederle takes every precaution during production and testing to ensure the safety of ORIMUNE. This dedication is evident by our 29-year safety record.

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Lederle has consistently met the nation's needs for oral polio vaccine for about 29 years. In fact, when all other US manufacturers discontinued the production of oral polio vaccine, Lederle has remained committed to this essential product and to the health of America's children.

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*Paralytic disease following ingestion of live poliovirus vaccines has been reported on rare occasions in individuals receiving the vaccine or in their close contacts.

Orimune®

Poliovirus Vaccine Live Oral Trivalent

Manufactured by:
Lederle Laboratories
A Division of American Cyanamid Company

Brief Summary

Poliovirus Vaccine
Live Oral Trivalent
ORIMUNE®

Please see package insert for full description, directions for use, and references.

INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*

CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*
Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in human immunodeficiency virus (HIV) infection, thymic abnormalities, leukemia, lymphoma, generalized malignancy or advanced debilitating conditions, or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. ORIMUNE should also not be given to members of a household in which there is a family history of immunodeficiency until the immune status of all members is determined to be normal. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*
Administration of the vaccine should be postponed or avoided in those experiencing any febrile illness or acute infection and in those with any advanced debilitated condition or persistent vomiting or diarrhea, or suspected gastroenteritis infection.

Other viruses (including poliovirus and other enteroviruses) may compromise the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis. **Records Required by the National Childhood Vaccine Injury Act:** Manufacturer and lot number of vaccine administered must be recorded by health care provider in vaccine recipient's permanent record, along with date of administration and name, address, and title of person administering vaccine.

Health care provider must report to a health department or to the FDA the occurrence following immunization of any event set forth in the Vaccine Injury Table including: paralytic poliomyelitis — in a nonimmunodeficient recipient within 30 days of vaccination — in an immunodeficient recipient within 6 months of vaccination; any vaccine-associated community case of paralytic poliomyelitis; or any acute complication or sequela (including death) of above events.

Use in Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with Poliovirus Vaccine Live Oral Trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. A large retrospective study suggests that OPV may be temporally associated with Guillain-Barré syndrome. A causal relationship has not been established. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts.

The Centers for Disease Control report that during the years 1973 through 1984 approximately 274.1 million OPV doses were distributed in the US. During this same period, 105 vaccine-associated cases were reported (1 case per 2.6 million doses distributed). Of these 105 cases, 35 occurred in vaccine recipients (1 case per 7.8 million doses distributed), 50 occurred in household and nonhousehold contacts of vaccinees (1 case per 5.5 million doses distributed), 14 occurred in immunodeficient recipients or contacts, and 6 occurred in persons with no history of vaccine exposure, from whom vaccine-like viruses were isolated.

Thirty-three (94%) of the recipient cases, 41 (82%) of the contact cases, and 5 (36%) of the immune deficient cases were associated with the recipient's first dose of OPV. Because most cases of vaccine-associated paralysis have occurred in association with the first dose, the CDC has estimated the likelihood of paralysis in association with first v subsequent doses of OPV, using the number of births during 1973-1984 to estimate the number of first doses distributed, and subtracting this from the total distribution to estimate the number of subsequent doses distributed. This method estimates a frequency of paralysis for recipients of 1 case per 1.2 million first doses v one case per 116.5 million subsequent doses; for contacts, one case per 1 million first doses v one case per 25.9 million subsequent doses; with an overall frequency of 1 case per 520,000 first doses v 1 case per 12.3 million subsequent doses.

Other methods of estimating the likelihood of paralysis in association with OPV have been described. Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults 2 doses of enhanced potency IPV a month apart before the children receive ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the second dose of enhanced potency IPV. A booster dose of enhanced potency IPV can be given to partially immunized adults at the same visit that the first dose of OPV is given to the child. The adult should be informed of precautions, such as handwashing after changing diapers.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults…[with IPV]…before giving OPV to the child."

The American Academy of Pediatrics and the American College of Physicians have made similar recommendations.

Rev. 1/91
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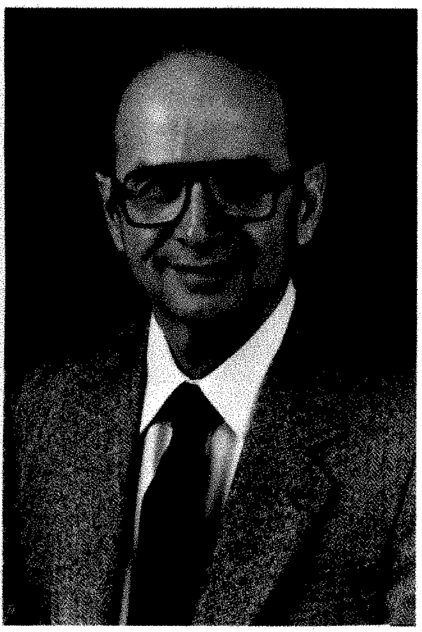

Milton Arnold, MD

The pediatrician is inundated with a plethora of continuing medical education opportunities, virtually on a daily basis, and has learned to be selective. It follows that program planners and faculty should be aware of the target audience, educational objectives, and optimal techniques in their presentation.

There are a generous number of very competent and knowledgeable physicians available in the academic and practicing community. From this group, a substantially smaller number should be selected who have the teaching skills appropriate for various settings, ie, those educators who can communicate effectively. Certain faculty and topics are better suited for different forums. The brief plenary may ill serve a subject that must have a basic science understanding included in its presentation. This is exemplified by molecular biology, which is best given in seminars. The faculty and registrants should know in advance the level of sophistication to be addressed. The speaker who chooses to talk more rapidly to conform to schedules or runs significantly over the allotted time is not appreciated. Some educators are superb in bedside teaching but "fizzle" in larger groups. The reverse is also true.

Large conferences can accommodate a greater spectrum of faculty and topics in a variety of forums, including plenary sessions (brief presentations on new therapies, controversies, and basically single topics), seminars of varying lengths, and workshops (with limited attendance) for hands-on learning.

The shorter conference (usually 1 to 3 days) is very popular, attracting individuals with time constraints, possibly combining education with recreation, and addressing an eclectic group of topics usually of general interest. These problems can be varied to include plenary as well as miniseminars and workshops.

Both types of presentations share common features and should be addressed with care. Audiovisual problems are the second most frequent complaint voiced by attendees. Even the sophisticated lecturer may have vintage slides that are ill conceived. Critiques from recent meetings include "print on slides too much and too small," "complicated graph," and "not current." Guidelines for preparing slides are readily available from most professional organizations. These materials need not be expensive and the composition can be enhanced by computer publishing devices. Simplicity and legibility are the requisites. When the slides are confusing or illegible and the lights in the auditorium are dimmed, rapid eye movement sleep rapidly ensues regardless of the skills of the speaker. The slides should contain one concept and generally have no more than six lines on a horizontal slide or nine on a vertical slide. They can usually be read when held in one's hand.

Since computers allow a rainbow of colors, there is a great temptation to mimic Picasso. Not all of the great masters were readily appreciated or understood. Limit the number of colors selected and choose those that amplify the others.

Here are some caveats: Do not be a reader, either from a manuscript or from slides. Highlight slides or graphs, but do not read them line by line. The audience can read. If one apologizes for the quality of the slide, it should not have been used. The skill of the speaker is not validated by the rapidity or number of slides presented. Edit in advance.

The audiovisual system, including pointers and remote control units, should be checked daily before the meeting. Remember that the same room may be used for another function and then improperly set up again. Often, conference sites are hotels that are much more suited for entertainment than lectures. It is imperative to know where the light controls are and how they can be modified. The lights should be dimmed just to the point at which the screen is easily visible. Blacked-out rooms are for resting and escape. The size and location of the screen must be appropriate for the setting. The speaker who tends to wander away from the podium or turns toward the slide should wear a portable lapel microphone.

Cover the material promised in the course abstract. Allow adequate time for questions if the program is so designed. Questions should be answered completely but in a succinct manner. Occasionally, members of the audience may have their own shopping list that is not of interest to the entire group. They should be invited to see you during breaks. Do not get involved in debates that are going nowhere. Remember, it takes practice to develop audience control skills.

Almost everyone appreciates humor. It makes a meeting more enjoyable, but it should not replace substance. Avoid statistical comments that are distracting, eg, there are 24 causes for "Blarney's" syndrome. The audience immediately adopts a Cape Canaveral countdown mode. They pay little attention to the speaker's current comments. Rather, they begin to count backwards . . . 24, 23 . . . until they reach "blastoff."

In preparing a lecture, establish the skills of the target group. For example, lectures on the rational use of imaging devices are eagerly accepted, but the complex physics that separate the computed tomographic scan, magnetic resonance imaging, and ultrasonography should be saved for a group of radiologists. Reviewing timeworn information is acceptable if it does not demean the audience. Periodic recycling has value, but new practical take-home pearls are most appreciated. Avoid the use of jargon that is unique to a subspecialty.

Skills may be improved by mingling with the audience during breaks. They will provide feedback that may be most helpful. Audiences enjoy meeting their faculty.

One pearl from a senior citizen—if you have been chosen to speak for 2 hours before a break, plan ahead . . . "fluids in, fluids out."

BOOK REVIEW

Advances in Pain Research and Therapy

Edited by Donald C. Tyler and Elliot J. Krane, 405 pp, $98, New York, NY, Raven Press, 1990.

The management of pain has become an increasingly important issue in pediatrics. During the last decade, information about the undertreatment of childhood pain has been disseminated along with information about new and effective pharmacologic and behavioral techniques to help children endure painful procedures.

The topics in this book encompass most of the key issues involving childhood pain. Sectional titles include: pain assessment/tools; the neonate; acute pain management/regional techniques; behavioral management; chronic nonmalignant pain; and cancer pain. In each section, different authors have contributed either review articles or reports of their research. The relevance of the research reports depends on the interest of the reader.

The section called "Pain Assessment/Tools" begins with an excellent review chapter. Most of the chapters that follow are research reports. It would have been helpful if the many different assessment tools mentioned in this section were discussed together somewhere else in the text. The next section, which discusses neonates, also starts with an excellent overview article. This section is a wonderful mix of theory, science, and assessment. "Acute Pain Management/Regional Techinques" is the most technical of the sections, with individual chapters describing varying regional anesthesia techniques. Because most health care providers use behavioral techniques to control pain, the section on behavioral management is particularly important and is well done. The chapters provide both an overview as well as sufficient specific information so that providers can begin to help children cope with pain. The last two sections, "Chronic Nonmalignant Pain" and "Cancer Pain" are specific to the problems addressed, and the relevance of these sections depends on the interests of the reader.

For health care providers interested in pediatric pain, this book is an excellent addition to the growing list of publications on the subject. The editors have chosen the broad categories carefully, the chapters are well written and referenced, and the information is important.

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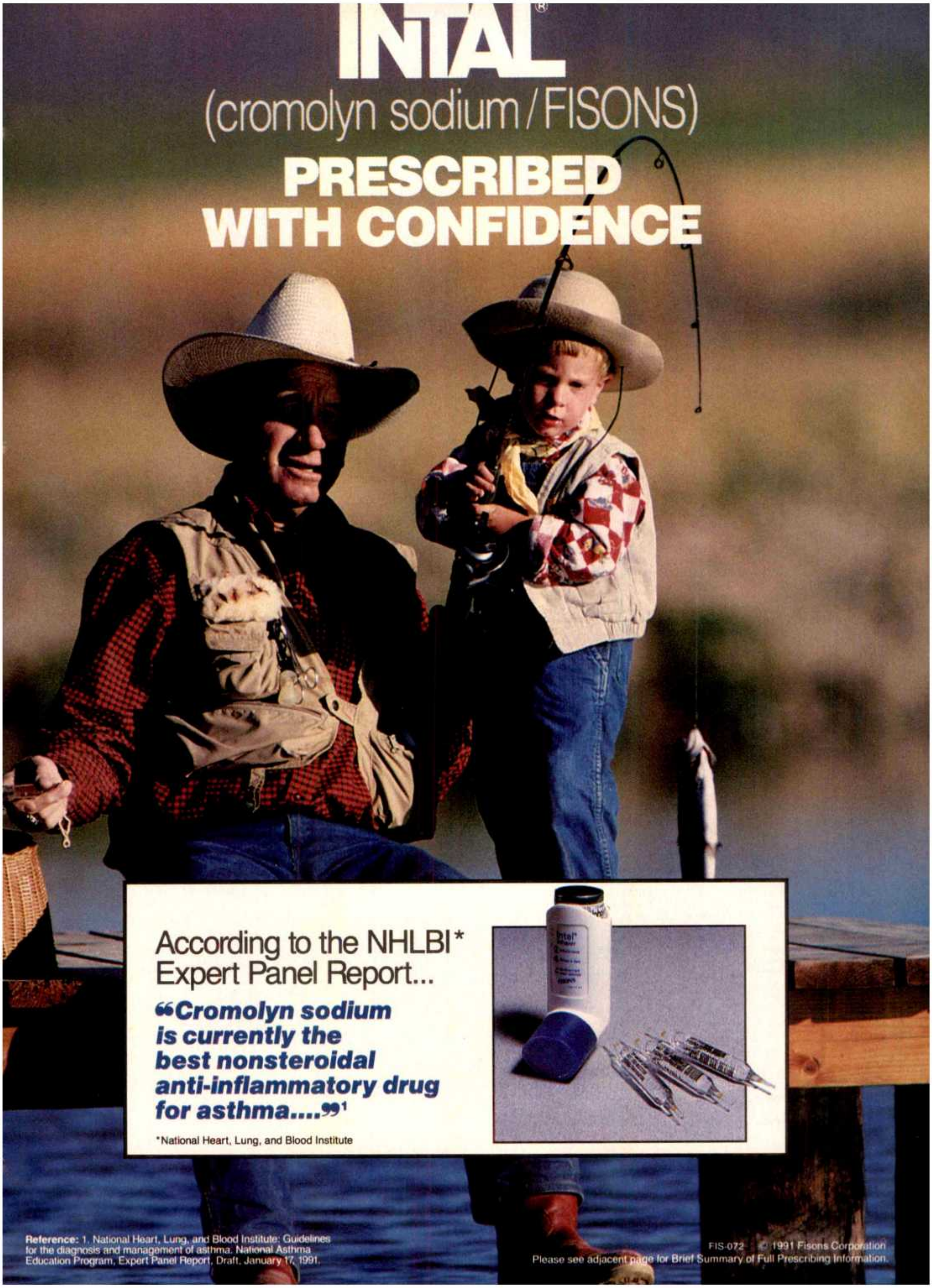

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According to the NHLBI* Expert Panel Report...

“Cromolyn sodium is currently the best nonsteroidal anti-inflammatory drug for asthma....”[1]

*National Heart, Lung, and Blood Institute

Reference: 1. National Heart, Lung, and Blood Institute: Guidelines for the diagnosis and management of asthma. National Asthma Education Program, Expert Panel Report, Draft, January 17, 1991.

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Please see adjacent page for Brief Summary of Full Prescribing Information.

INTAL Inhaler, 800 mcg/puff
(cromolyn sodium inhalation aerosol)

Brief Summary

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were:

Throat irritation or dryness
Bad taste
Cough
Wheeze
Nausea

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for: **Fisons Pharmaceuticals**
Rochester, NY 14623 USA

By: Health Care Specialties Division
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Pertussis in Adults

Tatsuo Aoyama, MD, MPH; Yoshinao Takeuchi, MD; Akira Goto, MD; Hidehito Iwai, MD; Yuji Murase, MD; Takashi Iwata, MD

• A survey was conducted of 89 households in each of which at least one patient with culture-confirmed pertussis had been detected. The source of infection was found to be an adult in 10 (11.2%) of the 89 households, and the rate of secondary attack was 19 (10.3%) of 185. Furthermore, a laboratory study disclosed 17 adults with subclinical pertussis; the subclinical infection rate was 17 (25.0%) of 68. When compared with pertussis in young children, the adult illness was generally less severe and had different clinical features. Adult pertussis showed neither leukocytosis nor lymphocytosis, but it produced anti–pertussis toxin antibody more quickly and higher levels of anti–filamentous hemagglutinin and agglutinin antibodies, and showed stronger growth inhibition of Bordetella pertussis. Although adult pertussis is usually unrecognized because of its different clinical and laboratory features, it is a significant health threat that requires some measures for disease control.

(*AJDC.* 1992;146:163-166)

When pertussis was a major cause of infant morbidity and mortality, before the introduction of immunization, cases of pertussis always occurred among adults in contact with affected children. However, adult pertussis was epidemiologically unimportant because of its relatively low incidence in comparison with cases in children. As the incidence of pertussis decreased dramatically with the widespread use of immunization, adult pertussis became a major source of infection.[1-4] The survey of intrafamilial spread of pertussis was started in 1981 mainly for the estimation of vaccine efficacy,[5] and many cases of adult pertussis were recognized. However, internists and pediatricians are still unlikely to consider a diagnosis of pertussis in adults with paroxysmal cough. This lack of suspicion has resulted in spread of the disease.[6] The present study was conducted to examine the importance of adult pertussis and its effect on spread of the disease in the family. In addition, the clinical and laboratory features of adult pertussis were examined in comparison with pertussis in children.

PATIENTS AND METHODS

Between 1984 and 1990, a survey was conducted of 89 households in which at least one patient with culture-confirmed pertussis had been identified. Information on the household of each patient with pertussis was obtained by interview at the clinic. The information included patient symptoms, the vaccination status of all family members, and the occurrence of any primary, coprimary, or secondary cases. For the purpose of this study, a case of pertussis was defined as development of a paroxysmal cough lasting for more than 2 weeks. Pertussis was further classified as follows. The *primary case* was the first case of pertussis in the household. A *secondary case* was a case of pertussis in the household with onset of symptoms occurring 1 to 4 weeks after onset of the primary case. A *coprimary case* was a case of pertussis in the household with onset of symptoms occurring within 1 week of onset of the primary case.

Among the 89 surveyed households, 203 adults were identified, of whom 99 (48.8%) agreed to participate in a bacteriologic and serologic study. Nasopharyngeal swabbing for *Bordetella pertussis* and blood sampling were performed at least once, irrespective of the symptoms. The nasopharyngeal swab was directly inoculated onto cyclodextron solid medium for isolation of the organism.[7] Anti–pertussis toxin (PT) IgG antibody and anti–filamentous hemagglutinin (F-HA) IgG antibody were measured by glass bead enzyme-linked immunosorbent assay.[8] Agglutinin titer for the serotype 1,3 strain was measured by microagglutination test, according to the procedure described by Manclark and Meade.[9] A fourfold or more increase in at least one of the three antibodies measured (anti-PT, anti-F-HA, and agglutinin) was considered to indicate serologic positivity.

The χ^2 test was used to evaluate the statistical significance of differences between proportions.

RESULTS

Among 203 adults in the 89 households, 37 adults with clinical pertussis were identified. The pertussis in these 37 adults included 10 primary cases, eight coprimary cases, and 19 secondary cases. The primary case occurred in an adult in 10 (11.2%) of the 89 households. A child with pertussis aged 1 year or younger was identified in 49 households, of which primary cases occurred in adults in eight households (16.3%). The secondary attack rate in adults was 19 (10.3%) of 185. Thirty-one (83.8%) of 37 adults with clinical pertussis and 68 (41.0%) of the remaining 166 agreed to participate in the laboratory

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Presented as a poster at the Sixth International Symposium on Pertussis, National Institutes of Health, Bethesda, Md, September 26, 1990.

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Table 1.—Signs and Symptoms of Pertussis in Adults and Children*

	Adults	Children
Protracted paroxysmal coughing attack (worse at night)	14 (100)	50 (100)
Shortness of breath during coughing attack	12 (86)	0 (0)
Tingling sensation in throat	12 (86)	0 (0)
Sleep disturbed by cough	8 (57)	50 (100)
Facial flushing by cough	3 (21)	45 (90)
Cough-induced vomiting	1 (7)	44 (88)
Whoop	1 (7)	20 (40)
Cyanosis with cough	0 (0)	20 (40)

*There were 14 adults and 50 children, aged 0 to 1 year, who showed culture-confirmed pertussis and typical symptoms, identified in 89 households.

study. Adults who participated were mostly those who brought their children with pertussis to the clinic. Nineteen (61.3%) of the 31 adults with clinical pertussis in whom bacteriologic and serologic tests were performed were confirmed to have positive results. Of these 19 cases, nine were confirmed by culture and serologic findings, five by culture alone, and five by serologic findings alone. Among the 68 adults without clinical pertussis who underwent the laboratory study, 17 cases of subclinical infection (25.0%) were identified (eight mildly symptomatic and nine asymptomatic infections). Of these 17 cases, five were confirmed by culture and serologic findings, six by culture alone, and six by serologic findings alone.

Although the majority of the 37 adults were uncertain of their immunization status and history of pertussis during childhood, three adults confirmed a history of pertussis immunization, and one had a history of pertussis in childhood. Of the 17 adults with subclinical infection, four had a history of pertussis immunization and one had a history of the disease.

To compare pertussis in adults and children in terms of clinical, hematologic, serologic, and bacteriologic features, 14 adults and 50 children with culture-confirmed pertussis were selected from the 89 surveyed households. Pertussis in adults was generally less severe than that in children. Also, the clinical signs and symptoms differed between adults and children (Table 1). The majority of adult patients complained of shortness of breath and a tingling sensation in the throat. In contrast, many children with pertussis suffered cough-induced vomiting, whoop, and cyanosis, which were rarely observed in adults.

Thirty-two blood samples from 14 adults with culture-confirmed pertussis and 120 blood samples from 50 children aged 1 year or younger with culture-confirmed pertussis in the surveyed families were examined. Marked leukocytosis with a leukocyte count of more than 15,000/mm315.0 × 10^9/L was observed in children during the initial 30 days after disease onset. However, no leukocytosis was observed in adults, with less than 50% lymphocytes observed in 30 of the 32 samples (Fig 1).

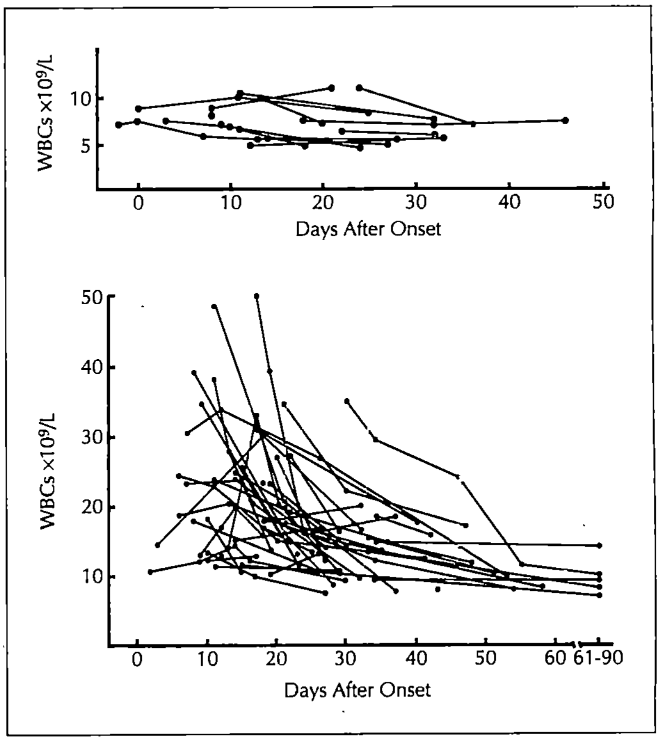

Fig 1.—*White blood cell (WBC) counts by days after disease onset in 14 adults (top) and 50 children aged 0 to 1 year (bottom) with culture-confirmed pertussis.*

During the initial 10 days after disease onset, anti-PT antibody responses were observed in adults but not in children. However, no differences in anti-PT antibody were observed between adults and children 11 days or more after the disease onset (Fig 2, top left and right). Anti–F-HA antibody responses were always much higher in adults than in children (Fig 2, center left and right). Agglutinin titer against serotype 1,3 tended to be higher in adults than in children (Fig 2, bottom left and right).

Amounts of colonies isolated before administration of erythromycin were compared between the 14 adults and 50 children. A standardized threefold streak method was employed, and the isolated colonies were categorized semiquantitatively from + to +++. The proportion of patients from whom large amounts of organisms were isolated before the administration of erythromycin (++ or +++) was significantly higher in children than in adults ($P<.05$) (Table 2).

COMMENT

In this study, adults were found to be responsible for 11% of infection sources. Particularly, in the households of patients with pertussis aged 1 year or younger, 16% of infection sources were adults. The adult secondary attack rate was 10%. Although the subclinical infection rate in vaccinated populations including children and adults was 55% in another family study,[10] the adult subclinical infection rate in the present study was 25%. Although adult pertussis used to be rare before the introduction of pertussis immunization, it has recently become more prevalent. The possible reasons for this prevalence are that, as the number of patients with pertussis decreased, chance of exposure to *B pertussis* was reduced and immunity against pertussis could not be fortified; and that immunity acquired by vaccination weakened faster than that acquired by natural infection.

Although the symptoms of pertussis are generally less severe in adults than in children, some adults with pertussis were admitted to the hospital because of severe coughing attacks. This means that pertussis in adults is a

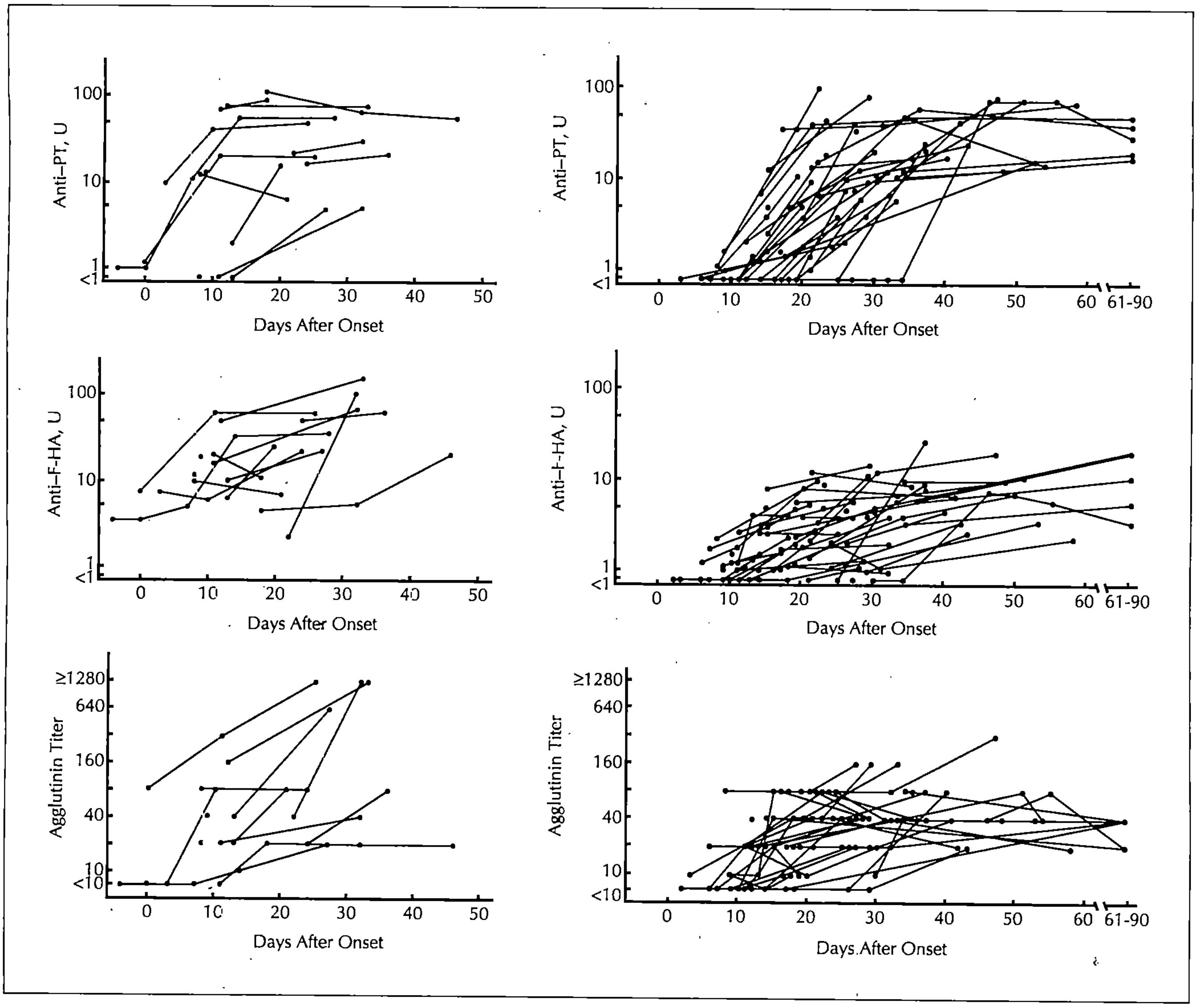

Fig 2.—*Anti-pertussis antibody responses by days after disease onset in 14 adults (left) and 50 children aged 0 to 1 year (right) with culture-confirmed pertussis. Top left and right, Anti-pertussis toxin (PT) antibody. Center left and right, Anti-filamentous hemagglutinin (F-HA) antibody. Bottom left and right, Agglutinin antibody for serotype 1,3.*

Table 2.—Adults and Children Aged 0 to 1 Year From Whom Large Amounts of *Bordetella pertussis Were Isolated Before Administration of Erythromycin**

	Days After Onset, No. (%) of Patients				
	0-10	11-20	21-30	31-40	Total
Adults	4/9	3/4	0/1	0/0	**7/14** (50)†
Children	16/20	18/20	6/8	1/2	**41/50** (82)†

*Rated + + or more. A standardized threefold streak inoculation method was employed. The isolated colonies were categorized semiquantitatively from + to + + +.

†$P<.05$.

health threat not only as a major source of infection for young children, but also because the clinical symptoms can sometimes be severe.[11] With respect to clinical features, protracted coughing attacks that worsen at night are the main symptom for both adults and children. In contrast, cough-induced vomiting, whoop, and cyanosis are frequently observed in children but are rare in adults. Adult patients often complain of shortness of breath and a tingling sensation in the throat. Awareness of these clinical characteristics is important for diagnosis of adult pertussis.

Leukocytosis and lymphocytosis, biologic manifestations of PT activity, are the main laboratory characteristics of children with pertussis. Neither leukocytosis nor lymphocytosis was observed in adults with pertussis. In terms of antibody responses, adults had more rapid anti-PT and higher anti-F-HA and agglutinin antibody responses. The number of isolated *B pertussis* organisms was significantly lower in adults. These differences between adults and children are thought to be due to the age factor or previous exposure to the organism.

In this study, a majority of adults were uncertain of their immunization status and history of pertussis. However, 21 children aged 9 to 14 years with culture-confirmed pertussis were identified among the 89 surveyed households. Among these 21 children, eight were unimmunized and 13 were immunized. Fifty blood samples were collected (data not shown), among which only three from unimmunized individuals and none from immunized individuals showed leukocytosis with leukocyte counts of more than 15,000/mm315.0 × 10^9/L. However, many blood samples from unimmunized patients aged 0 to 1 year with pertussis showed leukocytosis during the first 30 days after disease onset. Unimmunized children aged 0 to 1 year with pertussis showed more marked leukocytosis and lymphocytosis much more often than those aged 9 to 14 years. Furthermore, no immunized children aged 9 to 14 years showed leukocytosis and lymphocytosis. These two facts suggest that aging and immunization prevent the occurrence of leukocytosis and lymphocytosis, implying that neither leukocytosis nor lymphocytosis in adult pertussis is due to age, presensitization, or both. Anti-PT antibody responses of the 21 children aged 9 to 14 years were more rapid during the initial 10 days in the immunized group than in the unimmunized group. Anti–F-HA and agglutinin responses were similar between the two groups and comparable with those in adults. These data suggest that differences in anti–F-HA and agglutinin antibody responses between adults and young children are more dependent on age and that the brisk anti-PT antibody responses seen in adults with pertussis are due to presensitization and not to age.

The most important diagnostic factor for adult pertussis is simply to recognize that the disease does occur in adults. Pertussis should always be suspected in those who have a protracted cough. Because the white blood cell count is not helpful in diagnosis, culture and serologic studies are more reliable. Also, detection of adult pertussis in a family makes the diagnosis more firm, although it is difficult to diagnose pertussis in young infants because of their atypical symptoms.

Pertussis used to be a disease mainly of children. However, adults are now a major source of pertussis transmission. As the incidence of pertussis in the adult population is still unclear, it is difficult to advocate the introduction of pertussis immunization for all adults at this point. However, adults working in close contact with children, such as caregivers in day-care centers, schoolteachers, and staff in pediatric wards, are more likely to contract pertussis, and immunization for such individuals might be desirable.

We would like to thank Prof Mitsuru Osano, MD, for advice. We express our sincerest thanks to the pediatricians, nurses, and clinical microbiologists of Kawasaki Municipal Hospital, Kawasaki-shi and Fussa General Hospital, Fussa-shi, Tokyo, Japan, for assistance.

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Cerebrospinal Fluid Neurochemistry in Children and Adolescents With Obsessive-Compulsive Disorder

Susan E. Swedo, MD; Henrietta L. Leonard, MD; Markus J. P. Kruesi, MD; David C. Rettew; Samuel Listwak; Wade Berrettini, MD; Mark Stipetic; Susan Hamburger; Philip W. Gold, MD; William Z. Potter, MD, PhD; Judith L. Rapoport, MD (*Arch Gen Psychiatry.* 1992;49:29-36)

Pertussis Antibodies, Protection, and Vaccine Efficacy After Household Exposure

Jann Storsaeter, MD; William C. Blackwelder, PhD; Hans O. Hallander, MD, PhD

• During a randomized trial of acellular pertussis vaccines, significantly fewer recipients of a two-component vaccine (Japanese National Institute of Health [JNIH]-6) were diagnosed as primary or coprimary cases in households than either placebo recipients or those who received a monocomponent pertussis toxoid vaccine (JNIH-7). After household exposure to a culture-confirmed primary case, efficacy for JNIH-6 was estimated to be 35% (95% confidence interval, −14% to 57%) against any culture-confirmed disease and 58% (95% confidence interval, −6% to 84%) against clinical disease with 21 days or more of coughing spasms. The corresponding efficacy estimates for JNIH-7 were 67% (95% confidence interval, 32% to 80%) and 82% (95% confidence interval, 41% to 96%). Differences between the JNIH-6 and JNIH-7 vaccines in efficacy after household exposure were not statistically significant. No association could be established between protection against pertussis after household exposure and serum levels of IgG antibody to pertussis toxin or filamentous hemagglutinin in vaccinated individuals, in either study children or other household members.

(*AJDC*. 1992;146:167-172)

Studies in Japan have indicated that Japanese acellular pertussis vaccines are safe and efficacious.[1-4] A randomized, placebo-controlled efficacy trial of two acellular vaccines, developed by the Japanese National Institute of Health (JNIH), was conducted in Sweden during 1986 to 1987. The two-component vaccine JNIH-6 was used regularly in Japan, while the monocomponent vaccine JNIH-7 was an experimental preparation, made especially for the Swedish trial. The JNIH-6 vaccine contained 7.5 μg of protein nitrogen per milliliter each of formaldehyde-detoxified pertussis toxin (PT) and filamentous hemagglutinin (FHA), while JNIH-7 contained 12 μg of protein nitrogen per milliliter of detoxified PT. Because both vaccines had been shown to give satisfactory serologic response to PT after two doses, a two-dose rather than a three-dose schedule was chosen in the trial.[5,6] Both vaccines were 70% to 80% protective against typical or severe whooping cough.[5,7] Similar or higher efficacy estimates have been attributed to conventional whole-cell vaccines.[8,9]

Estimates of vaccine efficacy (VE) from studies of household exposure have generally been slightly lower than those obtained by other methods.[8,10] This may reflect inability of the vaccines to protect against heavy exposure or methodologic problems with household-based studies.[10] Household studies of whole-cell vaccines have produced VE estimates of approximately 50% to 60% in the United Kingdom,[8,11,12] compared with 70% to 90% in the United States.[13,14] High VE estimates have also been reported for acellular vaccines in Japanese household studies.[3,4,15] It should be noted that booster vaccinations are given in the United States and Japan but not in the United Kingdom.[8]

The present household study was conducted prospectively during the efficacy trial in Sweden. The aims of the household study were (1) to estimate vaccine efficacy after household exposure to a culture-confirmed case, using various clinical case definitions as well as definitions that required a positive culture in addition to clinical symptoms, and (2) to search for serologic correlates of protection against typical pertussis disease (defined as 21 days or more of coughing spasms) with a positive culture, and against any colonization with *Bordetella pertussis* (defined as a positive culture, regardless of symptoms).

SUBJECTS AND METHODS

Clinical Methods

The Swedish efficacy trial included 3801 study children aged 6 to 11 months at 13 study sites. At each study site, children were randomly allocated to one of the three study groups in blocks of eight; two in each block received placebo, three received JNIH-6, and three received JNIH-7. Study children received, with 2-month intervals, two deep subcutaneous injections of 0.5 mL of placebo or vaccine. The three study groups were comparable with respect to a variety of characteristics and prognostic factors.[5] All injections were given between February 3, 1986, and mid-June 1986.

Households of study children were under active surveillance for a mean of 16 months after the second injection, until the end of August 1987. During this period, parents were instructed to call a study nurse if a study child coughed for 7 days or more; if they suspected whooping cough in the household; if any specific symptom, such as whoops, coughing spasms, or cough with

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Reprint requests to Barnhälsovården, Drakenbergsgatan 39, S-117 41 Stockholm, Sweden (Dr Storsaeter).

vomiting, occurred in any household member; or if a physician diagnosed pertussis in the household. Study nurses were instructed to telephone each household monthly to interview parents about possible pertussis in the household. When pertussis was suspected in households, blood samples and nasopharyngeal cultures were obtained from study children, and clinical information was collected on standardized forms. Weekly telephone contact was then maintained until the last day of cough in the household.

An extended household study was undertaken at 12 of the 13 study sites during the last year of the trial, from September 1, 1986, to August 27, 1987. Households were identified through one or more members (index cases) who were suspected to have pertussis. If a positive culture for *B pertussis* was obtained in the household, permission was sought to collect nasopharyngeal cultures and paired blood samples from all household members, except from the person with the first culture-confirmed case. Only households with a culture-confirmed first (primary) case of cough were included in the analyses. A primary case may or may not have been an index case. Samples were collected as early as possible after obtaining a positive culture for *B pertussis* in households, irrespective of symptoms.

In accordance with official Swedish recommendations, erythromycin treatment was not used routinely for uncomplicated pertussis in children above 1 year of age, and erythromycin was not administered prophylactically to contacts above 6 months of age.

Cultures

Nasopharyngeal specimens were taken with cotton swabs tested for nontoxicity to *B pertussis* (Pernasal Swab, Medical Wire & Equipment, Corsham, England). The swabs were passed into the nasopharynx as far posteriorly as possible, rotated, and left for 5 to 15 seconds for thorough moistening, then immediately inoculated on selective charcoal agar plates (Oxoid CM 119, Basing Stoke, England) prepared according to the method of Regan and Lowe.[16] Finally, the swabs were inserted into transport tubes with 50% of the same agar for enrichment. Culturing was repeated after 1 week if the individual still had a cough and the first culture was negative.

Serologic Testing

Serologic assays in this study included enzyme-linked immunosorbent assays for IgG and IgA antibodies against PT and FHA, as well as the Chinese hamster ovary cell assay, which is specific for PT. Details of the serologic procedures are published elsewhere.[17]

Early ("acute") blood samples were taken from household members as soon as possible after exposure to culture-verified pertussis, and convalescent samples were taken 6 to 8 weeks later. In addition, some serum samples that had been collected from mothers during pregnancy, for assessment of immunity to rubella virus, were available for analysis.

Ethics

The trial was approved by the ethics committees at the Karolinska Institute, Stockholm, Sweden, and at Umeå, Uppsala, and Linköping (Sweden) Universities. Clearance for the use of human subjects was obtained from the US National Institute of Allergy and Infectious Diseases. Oral informed consent was obtained from the parents of each child.

Statistical Methods

The period of household exposure was defined as 40 days, beginning with the onset of cough in the primary case. Individuals with onset of cough 5 days or less after onset in the primary case were considered *coprimary* cases and were deleted from analysis.

Study children who were exposed at least 30 days after their second injection of vaccine or placebo, and were not primary or coprimary cases, were included in analysis of VE. The VE was estimated by $1-p_v/p_u$, where p_v and p_u are risks of disease in vaccinated and unvaccinated children, respectively. A 95% confidence interval (CI) for VE was calculated by the method of Thomas and Gart.[18]

Table 1.—Study Children in Households With a Culture-Confirmed Primary Case*

	No.			
	Placebo	**JNIH-7**	**JNIH-6**	**Total**
Exposed <30 d after 2nd dose and/or received only 1 dose	14†	10‡	15§	**39**
Primary case	22	19	5	**46**
Coprimary case	1	2	3	**6**
Included in efficacy analysis	16	26	19	**61**
Total	**53**	**57**	**42**	**152**

*Categories are hierarchical; children included in the first row are not included in rows for primary and coprimary cases.

†Includes seven primary and one coprimary cases.

‡Includes one primary and two coprimary cases.

§Includes two primary and one coprimary cases.

Proportions of primary or coprimary cases among recipients of JNIH-7 and JNIH-6, as well as proportions of cases after household exposure, were compared by the standard χ^2 test without continuity correction.[19] Correlations between antibody levels in preexposure and acute serum samples were measured by the Spearman Rank Correlation Coefficient.[20] Associations between antibody level and pertussis disease or colonization were assessed by the Wilcoxon Two-Sample Rank-Sum Test.[20] All P values correspond to two-sided tests, and $P<.05$ was considered statistically significant.

RESULTS

Study Population

During the trial, 152 households with a culture-confirmed primary case were identified, 88 of which were in the extended household study. Sixty-one of the study children in the 152 households were included in the analysis of VE, after exclusion of those who were primary or coprimary cases, received only one injection of vaccine or placebo, or were exposed to pertussis earlier than 30 days after their second injection (Table 1). The 88 households in the extended household study contained, besides study children, 287 other members, of whom 66 were primary or coprimary cases and 185 had blood drawn for analysis: 16 children born in 1979 through 1987 (preschool children), 17 children born in 1970 through 1978 (school-age children), and 152 adults born before 1970 (Table 2).

Among all study children in the trial, 923 placebo recipients, 1403 JNIH-7 recipients, and 1385 JNIH-6 recipients were observed and remained free of culture-verified pertussis for at least 30 days after the second injection. Of these, significantly more JNIH-7 than JNIH-6 recipients developed primary or coprimary cases of culture-confirmed pertussis (21 vs eight, $P=.02$) (Table 1). The proportion of primary or coprimary cases among children who received placebo was higher than that in either vaccine group (placebo vs JNIH-7, $P=.09$; placebo vs JNIH-6, $P<.001$).

Analysis of VE

The median time to household exposure for study children, beginning 30 days after the second injection, was

Table 2.—Household Members (Other Than Study Children) in Extended Household Study*

	No.			
	Preschool Children	School-Age Children	Adults	Total
Primary case	53	2	4	**59**
Coprimary case	3	0	4	**7**
No paired serum samples	8†	1	18	**27**
Paired serum samples	16	17	152	**185**
Total	**80**	**20**	**178**	**278**

*Categories are hierarchical; primary and coprimary cases are not included in the entries in the last two rows.

†Three of these children were young infants, 1 to 8 months of age, who received early erythromycin prophylaxis.

317 days (range, 67 to 464 days) for placebo recipients, 286 days (range, 80 to 469 days) for JNIH-7 recipients, and 258 days (range, 59 to 452 days) for JNIH-6 recipients. Estimates of VE after household exposure and 95% CIs, using several definitions of pertussis, are given in Table 3. The VE against any clinical disease with 21 days or more of coughing spasms, with or without a positive culture, was estimated to be 82% (95% CI, 41% to 96%) for JNIH-7 and 58% (95% CI, −6% to 84%) for JNIH-6. Estimates of VE against culture-confirmed disease with any cough were 67% (95% CI, 32% to 80%) for JNIH-7 and 35% (95% CI, −14% to 57%) for JNIH-6. None of the 61 study children had a positive culture without symptoms. None of the differences between vaccines in Table 3 were statistically significant.

Postvaccination Antibody Levels and Protection

The proportions of vaccinees who (1) had a positive culture for pertussis after household exposure and (2) had a positive culture and 21 days or more of coughing spasms were calculated for different levels of anti-PT IgG and anti-FHA IgG antibodies in postvaccination serum samples (Table 4). There was no evidence of a protective level of anti-PT antibody, and a similar result was obtained with the Chinese hamster ovary cell assay (data not shown). Among children who received the two-component vaccine JNIH-6, there was some indication of a trend toward lower risk of a positive culture in those with higher anti-FHA IgG antibody levels ($P=.08$), but there was no such trend for risk of positive culture and 21 days or more of coughing spasms.

Comparison of Preexposure and Acute Antibody Levels

Preexposure serum samples collected during pregnancy were available for 50 mothers in the extended household study. Preexposure and acute serum samples were significantly correlated for anti-PT IgG antibody level (Spearman $r=.77$) and anti-FHA IgG antibody level ($r=.70$). These correlations support the use of acute samples to indicate antibody levels at the time of exposure, at least in this age group. The acute samples were taken a median of 16 days (10th percentile, 9 days; 90th percentile, 31 days) after exposure.

Acute Antibody Levels and Protection

The preschool children were expected to be unvaccinated against pertussis, as routine pertussis immunization had been terminated in Sweden in 1979. Of the 16 preschool children from whom blood was drawn (Table 2), 15 were unvaccinated and one child had received two doses of whole-cell vaccine in infancy. Five of the children had 21 days or more of coughing spasms with whoops after household exposure; three of these five had positive cultures, including the one child who had previously received whole-cell pertussis vaccine. None of the five had detectable IgG antibodies against either PT or FHA in the acute sample. The remaining 11 preschool children had no coughing spasms. All 11 were reported by their parents to have had whooping cough earlier in life, and all 11 had detectable anti-PT and/or anti-FHA IgG antibodies in the acute sample (two had no detectable anti-PT, and two others had no detectable anti-FHA antibodies). Hence, in unvaccinated preschool children, the presence of anti-PT and/or anti-FHA antibodies was correlated with protection against clinical disease.

The school-age children were expected to be have been vaccinated against pertussis in infancy with Swedish whole-cell vaccine. None of the 17 school-age children from whom blood was drawn (Table 2) developed cough or had a positive culture after household exposure. Fifteen of the 17 had detectable anti-PT and/or anti-FHA IgG antibodies in the acute sample, including six who had been vaccinated in infancy according to the parents, five who both had been vaccinated and had had pertussis previously, three who had not been vaccinated and had previously had pertussis, and one who had not been vaccinated and had no history of pertussis. Both of the children with no detectable antibodies in the acute sample were reported to have received three doses of whole-cell pertussis vaccine in infancy and to have had no pertussis previously. Thus, in these children, most of whom had been vaccinated, there was no clear relationship between the presence of anti-PT or anti-FHA antibodies in the acute blood sample and protection against pertussis.

In adults, there was no evidence of an association between anti-PT IgG antibody level in the acute sample and protection against either (1) a positive culture for pertussis (one adult had a positive culture but no cough) or (2) culture-confirmed pertussis with 21 days or more of coughing spasms (Table 5). Similar results were obtained with the use of the Chinese hamster ovary cell assay (data not shown). Also in this age group, there was some indication of a trend toward lower risk of a positive culture in those with higher anti-FHA IgG antibody levels ($P=.17$, not statistically significant), but there was no such trend for risk of positive culture and 21 days or more of coughing spasms. Twelve of the adult household members had no detectable IgG antibodies against either PT or FHA in the acute sample. Two of the 12 had a positive culture for pertussis; both reported that they had received whole-cell vaccine in infancy, and one of the two claimed to have had whooping cough previously.

Antibody Rises After Household Exposure

Sensitive serologic criteria, which had been evaluated for young children,[17] were used in this analysis. Significant IgG and/or IgA antibody rises from the acute to the convalescent samples were common in exposed household members (Table 6). All who had positive cultures, including one asymptomatic adult, showed significant rises in paired serum samples in anti-PT IgG and/or anti-FHA IgG antibodies.

Table 3.—Vaccine Efficacy After Household Exposure to a Culture-Confirmed Primary Case, According to Case Definition*

Case Definition	Placebo (N=16) No. of Cases	JNIH-7 (N=26) No. of Cases	JNIH-7 (N=26) VE, % (95% CI)	JNIH-6 (N=19) No. of Cases	JNIH-6 (N=19) VE, % (95% CI)
All Cases					
Any cough	15	17	30 (−3-38)	14	21 (−13-31)
Any coughing spasm	14	7	69 (39-79)	9	46 (5-61)
≥14 d of coughing spasms	13	3	86 (60-95)	6	61 (19-78)
≥21 d of coughing spasms	10	3	82 (41-96)	5	58 (−6-84)
Coughing spasm and whoop	11	2	89 (58-98)	4	69 (19-89)
Culture-Confirmed Cases					
Any cough	13	7	67 (32-80)	10	35 (−14-57)
Any coughing spasm	12	6	69 (31-85)	7	51 (−1-73)
≥14 d of coughing spasms	11	3	83 (48-96)	5	62 (8-84)
≥21 d of coughing spasms	9	3	79 (32-95)	5	53 (−23-83)
Coughing spasm and whoop	8	2	85 (34-98)	4	58 (−27-88)

*JNIH indicates Japanese National Institute of Health; VE, vaccine efficacy; and CI, confidence interval.

Table 4.—Relationship Between Postvaccination ELISA IgG Antibody Level Against PT and FHA and Protection Against Pertussis Colonization (Positive Culture) and Disease After Household Exposure*

Postvaccination Antibody Level, ELISA U	No. (%) With Positive Culture	No. (%) With Positive Culture and ≥21 d of Coughing Spasms
	Anti-PT IgG†	
≤100	5/11 (45)	2/11 (18)
100-199	5/11 (45)	4/11 (36)
200-299	2/9 (22)	0/9 (0)
≥300	5/14 (36)	2/14 (14)
Total	**17/45 (38)**	**8/45 (18)**
	Anti-FHA IgG‡	
≤2	1/1 (100)	0/1 (0)
3-9	2/3 (67)	1/3 (33)
10-19	3/5 (60)	1/5 (20)
20-29	2/3 (67)	1/3 (33)
≥30	2/7 (29)	2/7 (29)
Total	**10/19 (53)**	**5/19 (26)**

*ELISA indicates enzyme-linked immunosorbent assay; PT, pertussis toxin; and FHA, filamentous hemagglutinin

†In 45 recipients of Japanese National Institute of Health (JNIH) vaccines 6 plus 7.

‡In 19 recipients of JNIH-6.

COMMENT

Household studies have been recommended for the assessment of VE against such disease as measles and pertussis, where high and relatively uniform exposure within the household can be assumed.[21] In addition, a household study was thought to be a valuable addition to the Swedish trial because all of the households were part of a randomized trial and complete ascertainment of households with culture-confirmed pertussis could in principle be achieved.

During the trial, most primary and coprimary cases among vaccinated children occurred in recipients of the monocomponent vaccine JNIH-7 (Table 1). Furthermore, during posttrial follow-up in 1987 through 1990, JNIH-6 showed statistically significant higher VE than JNIH-7 against culture-confirmed pertussis with more than 30 days of cough.[22] Randomization and the widespread possibility of exposure in a nonvaccinating community made it unlikely that the two vaccine groups were unequally exposed to pertussis during the trial. It is more likely that the two-component vaccine gives more protection against community exposure to *B pertussis*. Differences between the two vaccines in VE after household exposure were not statistically significant and may have been due to chance.

After household exposure, both acellular vaccines gave moderate protection against pertussis with at least 14 days or at least 21 days of coughing spasms (Table 3). Protection was lower when milder cases were included. This observation is consistent with earlier reports from the Swedish trial[5,7] and elsewhere[11] and with the hypothesis that pertussis vaccines are more likely to protect against clinical pertussis disease than against colonization per se.[8] These results do not allow a conclusion about the relative efficacy of acellular and

Table 5.—Relationship Between Acute ELISA IgG Antibody Level Against PT and FHA and Protection Against Pertussis Colonization (Positive Culture) and Disease After Household Exposure in 152 Adults*

Acute Antibody Level	No. (%) With Positive Culture	No. (%) With Positive Culture and ≥21 d of Coughing Spasms
	Anti-PT IgG	
≤5	3/44 (7)	0/44 (0)
6-19	3/47 (6)	2/47 (4)
20-39	1/24 (4)	1/24 (4)
40-59	0/13 (0)	0/13 (0)
≥60	3†/19 (16)	1/19 (5)
Total	**10/147 (7)**	**4/147 (3)**
	Anti-FHA IgG	
≤2	4/32 (13)	2/32 (6)
3-9	3†/47 (6)	0/47 (0)
10-19	3/36 (8)	2/36 (6)
20-29	1/15 (7)	1/15 (7)
≥30	0/20 (0)	0/20 (0)
Total	**11/150 (7)**	**5/150 (3)**

*Serologic results were not complete for all individuals. ELISA indicates enzyme-linked immunosorbent assay; PT, pertussis toxin; and FHA, filamentous hemagglutinin.

†Includes one who remained asymptomatic.

Table 6.—Significant IgG and/or IgA Antibody Rises Against PT or FHA in Paired Serum Samples After Household Exposure to *Bordetella pertussis**

	No. (%) With Significant Titer Rise	
Age Group	Positive Culture	Negative Culture and No Cough
Study children	30/30 (100)	6/10 (60)
Preschool children	3/3 (100)	3/6 (50)
School-age children	0/0 (0)	8/17 (47)
Adults	11/11 (100)	43/117 (37)
Total	**44/44 (100)**	**60/150 (40)**

*PT indicates pertussis toxin; FHA, filamentous hemagglutinin.

whole-cell vaccines, either for disease of long duration or for mild disease. Such a conclusion must await a direct comparison in a trial that uses identical and unbiased case ascertainment techniques.

Previous pertussis immunization may reduce the chances of obtaining a positive nasopharyngeal culture.[7,23] However, in this study, similar proportions of placebo and vaccine recipients with coughing spasms also had positive cultures, whether the spasms were of long or short duration (Table 3). This finding may be a reflection of intense and prolonged exposure within households and of the early and aggressive case ascertainment in the household study.

The VE after household exposure of the two-component vaccine JNIH-6 against clinical disease with 14 days or more of coughing spasms was estimated to be 61% (95% CI, 19% to 78%). Aoyama et al[24] obtained an estimate of 77% (95% CI, 0% to 96%) with the use of the same clinical case definition in a Japanese household study of the same vaccine. Considering the small numbers of subjects and resulting wide CIs in both studies, these estimates are reasonably comparable. However, VE estimates from the present study are much lower than estimates from other Japanese household studies.[3,4,15] Differences between these studies and the Swedish study are considerable. The Japanese studies included two-component and multicomponent vaccines, and Japanese children routinely received a series of three primary doses of acellular pertussis vaccine beginning at 2 years of age, with a booster dose 1 year after the third dose.[3] The Swedish study children received two doses of one- or two-component vaccine starting at 6 to 11 months of age, with no booster. Finally, methodologic differences in case ascertainment and follow-up between household studies in different parts of the world are great, and the possibility of ascertainment biases makes direct comparisons problematic.[8]

Possible serologic markers of protection in recipients of whole-cell pertussis vaccines after household exposure have been studied in the past. Investigators in two studies during the 1940s concluded that the presence of agglutinins in titers of 1:320 or more (by macrotechnique) always conferred protection and that many vaccinated children without detectable agglutinins were also protected.[25,26] In the present study, the absence of IgG antibodies against PT or FHA was associated with susceptibility to pertussis disease among unvaccinated children. However, the study gives little support for the concept that pertussis is solely or primarily a PT-mediated disease.[27] No association was found between postvaccination IgG antibody levels against PT and protection for vaccinated study children (Table 4), or between acute anti-PT IgG antibody level and protection for adult household members (Table 5).

Immediate preexposure serum samples would be ideal for studying the association between antibodies and clinical protection, but such serum samples are not easily obtained. Exposed, vaccinated study children in Sweden were shown to have very rapid booster responses, even before the beginning of cough.[17] Antibody levels in acute serum samples therefore cannot be expected to reflect the preexposure levels in young vaccinated children. In adults, however, antibody levels in blood samples taken relatively early after exposure seem to reflect preexposure levels, both in our study and elsewhere.[28]

The IgG antibodies against PT may contribute to protection, but they are also markers for other possibly protective antibodies acquired as a result of vaccination or exposure to pertussis,[29] including antibodies against agglutinogens and a 69-kd outer membrane protein called pertactin.[28,30] Antibodies against these other proteins were not measured in the present study. Cellular immunity is also likely to play a role in protection.[31]

Antibody rises were common among both symptomatic and asymptomatic household contacts of pertussis cases. This is consistent with findings in other reports.[28,32,33]

Most of the serologic results from this household study are based on small samples of subjects. Criteria for inclusion in these analyses were determined beforehand, for the purpose of decreasing bias. Still, trends or differences may be due to chance or unrecognized bias.

We conclude that the two-component vaccine was more protective against community exposure to pertussis, and that both vaccines were moderately protective under conditions of household exposure. Protection against pertussis disease with 21 days or more of coughing spasms was not associated with the postvaccination anti-PT or anti-FHA antibody levels. In adults, acute antibody levels were correlated with preexposure levels, but no association was found between acute anti-PT or anti-FHA levels and protection against pertussis disease.

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Pertussis Outbreaks in Groups Claiming Religious Exemptions to Vaccinations

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• **Four recent outbreaks of pertussis in Massachusetts illustrate some features that contribute to the increased incidence of the disease. The outbreaks involved unimmunized groups of children with philosophical or religious exemptions from school or day-care immunization requirements and children and adults who were reluctant to undergo antibiotic prophylaxis or therapy. Parents and physicians should be aware that failure to immunize and to cooperate in follow-up preventive measures can have public health and potential medicolegal repercussions.**

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Between 1981 and 1988, the incidence of pertussis in the United States increased almost threefold, from 0.5 cases per 100 000 in the population to 1.4 cases per 100 000 in the population.[1,2]

Four pertussis outbreaks that occurred in Massachusetts between 1986 and 1988 help illustrate two factors that may be contributing to the spread of the disease: (1) groups of susceptible school-aged children who are not vaccinated due to broad interpretations of religious and philosophical exemptions from immunization statutes; and (2) the reluctance of children and adults to undergo antibiotic treatment or prophylaxis.

PATIENTS AND METHODS

Each outbreak of pertussis was recognized during the course of routine surveillance and follow-up of clinically diagnosed or laboratory-confirmed cases.

Outbreak 1 (August through September 1986).—Investigation of a case identified by application of a positive fluorescent antibody smear revealed a symptomatic sibling who was enrolled in a private school, which was both a licensed day-care center and an accredited elementary school. Approximately half of the students had a persistent cough at that time.

Outbreak 2 (May through July 1987).—Investigation of a 3-year-old symptomatic child with a positive fluorescent antibody smear revealed several other symptomatic children in a play group.

Outbreak 3 (November through December 1987).—Follow-up of an 18-month-old child with culture-confirmed pertussis revealed a symptomatic older sibling who was a student at a private school. On notification, school officials identified seven other symptomatic students.

Outbreak 4 (October through November 1988).—Two clinically diagnosed patients with pertussis attended the same private school. School officials confirmed that other students were experiencing similar illnesses.

To control the spread of the disease, the following measures were undertaken: (1) all students and staff members of each school as well as members of the play group were advised to initiate erythromycin estolate prophylaxis and continue treatment for at least 10 days; (2) symptomatic students and staff members and symptomatic members of the play group were excluded from school or the play group until 7 days of prophylaxis had been completed; (3) anyone refusing to undergo antibiotic prophylaxis was excluded from school or the play group until 21 days after the most recent exposure; (4) prophylaxis was advised for all household contacts of symptomatic individuals; (5) other institutions, eg, day-care centers, schools, hospitals, and businesses, at risk of exposure due to the cases identified in each outbreak were informed of the existence of cases and given surveillance and control advice; and (6) area health-care providers were informed of the existence of cases and reminded to report any they might diagnose.

To assess the extent of acceptance of antibiotic treatment for patients and prophylaxis for contacts, a comparison group of patients and their contacts were selected from the Massachusetts Department of Public Health (MDPH) Pertussis Case Registry. Cases were included in the comparison group if both their onset of symptoms and case reports to the MDPH were in the same calendar year as those from these outbreaks, and patients were matched by age (plus or minus 2 years for those at least age 2 years and plus or minus 6 months for those younger than age 2 years) to ensure that both groups would have similar age distributions. One-to-one matches were made.

A patient was defined as (1) an individual with a smear, culture, and/or serologic results positive for *Bordetella pertussis* (Diagnostic and Biologic Laboratories, MDPH, Jamaica Plain, Mass), or (2) an individual with a minimum of 2 weeks of coughing or at least 7 days of paroxysmal coughing and an epidemiologic link to a laboratory-confirmed case.[3]

RESULTS

The immunization status of patients and the diagnostic testing performed in each outbreak are summarized in Tables 1 and 2, respectively.

Outbreak 1

The 25 patients with pertussis ranged in age from 2 to 60 years (median, 4.5 years). Eight cases (32%) occurred in adults (age greater than 18 years).

The index patient was a 60-year-old physician who worked in a local hospital and who had no apparent ex-

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Table 1.—Immunization Status of Pertussis in Children in Four Outbreaks in Massachusetts, 1986-1988

	Total No. of Cases	Patients Younger Than 18 y	No. (%) of Patients Immunized	No. (%) of Patients Claiming Exemption	No. (%) of Patients Underimmunized	P
Outbreak 1 (8/11/86 to 9/28/86)	25	17	5 (29)	10 (59)	2 (12)	.35
Outbreak 2 (5/1/87 to 7/8/87)	26	21	3 (14)	17 (81)	1 (5)	.61
Outbreak 3 (11/1/87 to 12/18/87)	16	14	1 (7)	13 (93)	0	.009
Outbreak 4 (10/20/88 to 11/28/88)	46	44	7 (16)	32 (73)	5 (11)	.002
Total	**113**	**96**	**16** (17)	**72** (75)	**8** (8)	. . .

Table 2.—Diagnostic Testing in Four Outbreaks of Pertussis in Massachusetts, 1986-1988

	Fluorescent Antibody		Blood Culture		Serologic Examination	
Outbreak	No.	No. Positive	No.	No. Positive	No.	No. Positive
1	16	4*	4	3	2	2
2	10	6*	10	6	0	. . .
3	3	3	3	3	0	. . .
4	25	7	32	2	0	. . .

*Negative specimens were taken either more than 21 days after onset or after initiation of antibiotic therapy.

posure to pertussis. He had a persistent cough the previous month and his pertussis was serologically confirmed. He was the source of infection for his granddaughter who in turn transmitted pertussis to four children in her playgroup and two adults. Two of the children in the granddaughter's play group attended private school with her. Because of extensive contacts in and outside of school, there were multiple sources of exposure for 16 subsequent cases. Sixteen (64%) of the 25 patients were associated with the private school. This included 11 students (among 49 enrollees) and five teachers (among a staff of six). The students ranged in age from 3 to 8 years and the adults ranged in age from 24 to 39 years. Approximately 49% (24 of 49) of the schoolchildren were from families who incorporated a macrobiotic diet into their life-style. Based on these dietary beliefs, the families claimed religious exemptions from pertussis vaccinations.

Cases occurred in each of the six classrooms. Attack rates in the classrooms ranged from 10 per 100 to 80 per 100, with an overall attack rate of 22.4 per 100 students. Attack rates were not significantly different between underimmunized students (27 per 100) and immunized students (19 per 100) ($P = .3481$, Fisher's Exact Test). Since five (83%) of six teachers were symptomatic and had to complete 7 days of antibiotic therapy before returning to school, administrators voluntarily closed the school for 1 week.

Outbreak 2

Twenty-six cases were identified. Ages ranged from 9 months to 44 years (median, 4 years). Twenty-one (81%) of 26 occurred in children.

This outbreak was recognized in the middle of June following laboratory confirmation of one case. Since school and day-care programs were already closed for the summer, immunization laws and regulations for isolation of patients, quarantine of contacts, and use of antibiotic prophylaxis could not be enforced in control strategies. Despite a concerted effort to educate those involved and obtain voluntary cooperation concerning treatment and antibiotic prophylaxis of contacts, compliance was poor.

Outbreak 3

Sixteen cases were identified in this outbreak that occurred in children and adults aged 15 months to 35 years (median, 5 years); two (13%) were adults and 14 (88%) were children, 13 of whom had claimed religious exemptions or were unimmunized against pertussis.

The most likely index case was a kindergarten student whose onset of symptoms was on November 7, 1987. Two siblings and a classmate had onset of symptoms less than 2 weeks later. The infection then spread to other classmates and family members. When given guidelines regarding the need for antibiotic prophylaxis, the school administration decided instead to close the school 1 week early and delayed reopening 1 week to allow for one incubation period to pass while closed.

Seven (44%) of the 16 patients were students at the school in which 47 (36%) of 130 students had claimed religious exemptions to pertussis vaccination. Six (86%) of these seven students had been exempted from such vaccinations. Thus, the risk of illness among unvaccinated students was 10.6 times greater than that among immunized students ($P = .009$, Fisher's Exact Test).

Outbreak 4

Forty-six cases of pertussis were identified in this outbreak, two (4%) of which occurred in adults. Thirty-six (78%) patients were students at the school; four (9%) were siblings; four others (9%) were friends; and two (4%) were parents (one was a teacher at the school and the other was a member of the school's board of directors). Because of the closely knit nature of this school's community, there were multiple opportunities for exposure.

School immunization records indicated that 115 (55.6%) of the 207 students were not age-appropriately immunized against pertussis. Students who claimed religious

Table 3.—Antibiotic Treatment and Prophylaxis of Pertussis in Outbreak-Associated Patients and Their Contacts and Comparison Patients and Contacts, Massachusetts, 1986-1988

	No. of Patients		No. of Contacts	
Outbreak	Total	No. Treated With Antibiotics	Total	No. Who Received Prophylactics
Outbreak groups				
1	24	14	40	20
2	26	11	32	5
3	14	7	18	9
4	7	0	21	0
Total	71	32	111	34
Comparison groups				
1	8	7	26	11
2	12	8	17	15
3	12	11	17	13
4	7	7	23	13
Total	39	33	83	52

exemptions from pertussis immunizations had an attack rate that was 3.3 times greater than those who had been immunized ($P \leq .002$; confidence interval, 1.5 to 7.2). Students in classrooms with immunization rates lower than 50% were 3.1 times more likely to be a case than students in classrooms with higher immunization rates ($P = .002$; 95% confidence interval, 1.5 to 6.5). School administrators closed the school from December 2, 1988, until January 3, 1989, because only a minority of students were receiving antibiotic prophylaxis. A letter was sent home with students advising the families of the need for self-quarantine during the holiday season, especially if family members had a persistent cough. Attempts to do follow-up interviews with patients were not successful due to reluctance by the community to participate in the investigation.

Cooperation with control recommendations differed between members of these outbreaks and other patients and their contacts selected from MDPH records (Table 3). Only 32 (45%) of 71 outbreak patients were treated with antibiotics, while 33 (85%) of 39 control patients were treated ($\chi^2 = 14.69$, $P = .00013$). Similarly, 34 (31%) of 111 outbreak-associated contacts and 52 (63%) of 83 control contacts received prophylactic antibiotics ($\chi^2 = 18.03$, $P = .00002$).

COMMENT

Key measures in preventing pertussis are immunization and judicious use of prophylactic antibiotics. Pertussis can be prevented in children by immunization. Unfortunately, controversy over the safety of the pertussis vaccine has reduced acceptance. Highly publicized accounts of reactions to the vaccine and a dramatic increase in the number of malpractice lawsuits have made physicians and parents wary of using the diphtheria-tetanus toxoid and pertussis vaccine.[4-6] This publicity may have caused overinterpretation of the guidelines for medical contraindications.[7] However, this overinterpretation creates its own risk for malpractice if a child given an inappropriate medical contraindication suffers damage due to disease.[8] Pediatric diphtheria-tetanus toxoid adsorbed usage in Massachusetts increased from 1022 to 15 000 doses between 1982 and 1989 (MDPH Immunization Program). Thus, in addition to a pool of susceptible adolescents and adults, a growing cohort of children are not being vaccinated against pertussis or are not receiving a complete series of five immunizations of the diphtheria-tetanus toxoid and pertussis vaccine.

As demonstrated by these outbreaks, some children are not being vaccinated against pertussis disease because of an inappropriate vaccine-specific use of religious and philosophical exemptions allowed by state immunization laws. Those outbreaks are in contrast with other outbreaks of vaccine-preventable diseases, such as measles occurring primarily in urban areas, where passive underutilization or unavailability of immunization services are a major risk factor.[9-12] In the outbreaks reported herein, the majority of children with claimed religious exemptions were appropriately immunized for age against measles, mumps, rubella, and polio. Almost all also had received their full complement of diphtheria-tetanus toxoids. The exemptions were pertussis-specific. Although fewer than 1% of all Massachusetts kindergarten students claim religious exemptions to immunizations in yearly surveys since 1976, experience has been that such students are often clustered, creating susceptible groups capable of supporting outbreaks. Similar situations are likely to be present in other states. A revised system for monitoring individual schools' immunization rates through development of a computer program that identifies schools with more than 2% exemptions has helped identify those schools that need to be closely monitored for vaccine-preventable disease outbreaks.

The reluctance of many people involved in these outbreaks to undergo antibiotic treatment or prophylaxis hampered control efforts. Administration of antibiotics is the primary means of preventing disease transmission. While concerns about gastrointestinal distress interfere with erythromycin compliance, significant adverse effects are rare. Even with the increased risk of hepatic dysfunction among adults, the estolate formulation of erythromycin is preferred by some authorities.[13-14] Refusal to use antibiotics enhances the potential for continued transmission.[15] In these outbreaks, refusal of prophylactic therapy may have augmented the spread of infection.

A solution to the problems discussed herein may lie in development of an acellular pertussis vaccine licensed for use in the United States. Experience with such vaccines elsewhere suggests a diminished rate of reactions with comparable vaccine efficacy.[16] An improved pertussis vaccine may diminish the inappropriate application of the religious exemption clause written into most state immunization laws. If such exemptions continue to increase, even wider and more generalized outbreaks of pertussis similar to those seen in the prevaccine era may occur in the United States. This has already happened where public fears resulted in a decrease in pertussis vaccination.[17,18] Better tolerated vaccine in older children and adults may also allow for routine boosters of pertussis, along with the 10-year tetanus and diphtheria toxoid boosters in older children and adults. This holds the promise of reducing the clinical and epidemiologic problems presented by pertussis in adults.

Until new vaccines that are at least as immunogenic but demonstrably less reactogenic are available, it is up to practitioners and public health authorities to educate the public about the risks and benefits of pertussis vaccination for children.[15] Health-care providers must also realize the potential for pertussis to occur in adults as well as in children and take appropriate diagnostic and prophylactic steps to reduce the spread of disease.

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Children in Hiding

Writing about the children is the hardest part, because these are just words. I am not a woman of letters—and I cannot make the words cry out. So many children died of hunger, so many were gassed . . . so many, so many. . . .

There were live children too. Few of them were with their parents. They were already grown up, with that maturity of five- or six-year-olds which taught them that you must never cry, that you must never talk, and that almost all day you have to lie in bed.—Adina Blady Szwajger, MD, pediatrician in the 1944 Warsaw Uprising

Szwajger AB. *I Remember Nothing More: The Warsaw Children's Hospital and Jewish Resistance.* New York, NY: Pantheon Books Inc; 1990:136-137.

Prevention of Secondary Transmission of Pertussis in Households With Early Use of Erythromycin

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• To examine the effectiveness of erythromycin therapy and prophylaxis for pertussis, 17 households with one secondary case or more were compared with 20 households without secondary cases following a community-wide pertussis outbreak in Maricopa County, Arizona, in 1988. There were no significant differences between the two household groups in age distribution of members, size, crowding, race, proportion of children aged 7 months to 18 years with three or more diphtheria and tetanus toxoids and pertussis vaccine doses, or in the age distribution, vaccination status, or medical care of patients with primary cases. However, median intervals from onset of illness in primary cases to initiation of erythromycin therapy (for cases) and prophylaxis (for contacts) were 11 and 16 days, respectively, in households without secondary spread, vs 21 and 22 days, respectively, in households with secondary spread. These results provide additional evidence that erythromycin is effective in the medical management of pertussis and should be initiated promptly to minimize secondary spread.

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Although the reported incidence of pertussis declined markedly following the introduction and widespread use of diphtheria and tetanus toxoids and pertussis (DTP) vaccine in the 1940s,[1,2] it has remained relatively constant during the past 15 years. While the majority of cases occur among unvaccinated or partially vaccinated infants and preschool children, an increase in the age-specific incidence of pertussis among older children, adolescents, and adults has recently been observed.[2] This may be due in part to the low prevalence of natural infection and decline in vaccine-induced immunity, which has been reported to occur as early as 3 years following a primary series of three doses.[3,4]

Partial immunity may also result in milder, attenuated disease in previously vaccinated persons[5,6] and may increase the risk of inadvertent introduction of pertussis into households and other settings in which adolescents and adults are in frequent close contact with infants and young children, groups at highest risk for severe pertussis disease and its complications. Because the currently available whole-cell pertussis vaccine is only recommended for individuals younger than age 7 years,[7,8] alternative preventive measures must be sought for older age groups. Although chemoprophylaxis with erythromycin for household and other close contacts of patients with pertussis has been suggested, continued disagreement about its efficacy and optimal use and consequent lack of uniform recommendations[7,8] have limited widespread adoption of this measure.

In 1988, a statewide pertussis outbreak of 522 cases occurred in Arizona, 20% of which were culture confirmed. Although cases were reported from 12 of Arizona's 15 counties, 295 (57%) occurred in Maricopa County (metropolitan Phoenix), where the outbreak began in June and reached its height in late September and October. Although the incidence of disease was highest in children younger than age 1 year (312 cases per 100 000 individuals), persons aged 7 years and older accounted for 40% of cases. This setting provided an opportunity to study a large number of affected households in Maricopa County to determine risk factors for secondary spread and, more specifically, to examine the effectiveness of erythromycin treatment and prophylaxis.

PATIENTS AND METHODS

Case Ascertainment and Selection of Case Households

Pertussis cases were identified by the Maricopa County Health Department from investigation of all reports of suspected pertussis from physicians and other health care providers, self-reports, and follow-up of patients who had nasopharyngeal specimens submitted to the Arizona State Laboratory for pertussis culture.

Households located in Maricopa County having at least one member who was reported to have a suspected case of pertussis or had a nasopharyngeal specimen submitted for culture and had cough onset between July 1, 1988, and October 31, 1988, were eligible to be interviewed for the study. All suspected cases

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Preliminary results were presented in part at the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Houston, Tex, September 19, 1989.

Reprint requests to the National Center for Prevention Services, Centers for Disease Control, 1600 Clifton Rd, Atlanta, GA 30333 (Information Services).

were investigated to determine whether the household met these criteria. One-person households were excluded.

Questionnaire

To obtain information on household characteristics and pertussis disease status of household members, a standardized questionnaire was pretested and administered by telephone with the assistance of the Maricopa County Survey Data Center during October and November 1988. For nine households without working telephone service, home visits were conducted by study team members. The adult most familiar with the health status of all household members was interviewed. Information was collected on sociodemographic characteristics, DTP vaccination status, cough illness, and therapeutic and prophylactic measures, including type and duration of antimicrobial use, if any. Information on specific antimicrobial preparations and dosage was not collected.

Respondents were asked to refer to calendars during the interviews, and questions were related to specific events, such as Labor Day, or days that were noteworthy for respondents. Dates from the case report and follow-up investigation forms were used when respondents could not recall or were uncertain of dates of therapy or symptom onset. Follow-up interviews were conducted for households in which any member had had onset of symptoms within 2 weeks before the initial interview to determine duration of symptoms and whether any new cases had occurred. In addition, follow-up telephone calls were made to households in which members were still taking erythromycin at the time of the interview to determine the total reported number of days of erythromycin treatment or prophylaxis.

Definitions

A case of pertussis was defined as a positive nasopharyngeal culture for *Bordetella pertussis*, an acute cough lasting 14 or more days, or paroxysmal cough of 7 or more days' duration. This clinical case definition was previously shown to be both sensitive and specific in identifying culture-confirmed cases during pertussis outbreaks in Wisconsin and Delaware.[9]

Household members were classified according to the following criteria[5,10]: a primary case was defined as one in which the household member met the case definition with the earliest date of cough onset; a *coprimary* case was one in which the patient had cough onset within 1 to 6 days of the primary patient; a *secondary* case was one in which the patient had cough onset between 7 and 28 days after cough onset in the primary patient; and a *second primary* case was one in which the patient had cough onset more than 28 days after a primary, coprimary, or secondary patient in the same household. All other household members were classified as *nonpatients.*

Households with only a single pertussis case were classified as households with no secondary spread. Households in which secondary cases occurred were classified as households with secondary spread. Erythromycin treatment was defined as at least 5 days of continuous erythromycin administered for cough illness. Prophylaxis was defined as at least 10 days of erythromycin administered after exposure to prevent illness. These intervals were chosen based on earlier studies of eradication of the organism from the nasopharyngeal tract and prevention of subsequent illness in exposed contacts.[11,12]

Analysis

Characteristics of households with no secondary spread were compared with those of households with secondary spread using Yates' continuity-corrected χ^2 analysis, Fisher's Exact Test, and Wilcoxon's rank sum test, where appropriate.

RESULTS

Cases Meeting Eligibility Requirements

Of the 295 suspected cases of pertussis reported in Maricopa County during 1988, 149 (51%) occurred during the reference period for the study (July 1 to October 31) and had been reported in time to be considered for inclusion. Twelve (8%) of these 149 cases were subsequently excluded from consideration because they failed to meet the remaining eligibility requirements for the study (n = 3) or were excluded inadvertently (n = 9), leaving a total of 137 reported cases in 91 households eligible for interview. The sociodemographic characteristics of these 137 patients did not differ significantly from those reported outside the reference period for the study.

Table 1.—Primary and Secondary Cases of Pertussis in 37 Households

Age Group	No. of Members*	Primary Cases† No.	Primary Cases† AR, %	Secondary Cases† No.	Secondary Cases† AR, %‡	All Cases† No.	All Cases† AR, %
<6 mo	13	5	38	6	75	11	85
6-11 mo	5	3	60	2	100	5	100
1-4 y	39	10	26	8	28	13	46
5-9 y	30	9	30	3	14	12	40
10-14 y	15	2	13	2	15	4	27
15-18 y	6	1	17	1	20	2	33
19-39 y	63	6	10	7	12	13	21
≥40 y	13	1	8	0	0	1	8
Total	**184**	**37**	**20**	**29**	**20**	**66**	**36**

*Excludes five members whose ages were not known.

†AR indicates attack rate.

‡Primary cases were excluded from the denominator.

Household Attack Rates

Of the 91 households that met eligibility requirements for entry into the study, 84 interviews (92%) were completed; 71 households had at least one member who met the case definition, including an additional 35 patients whose cases had not been reported previously. To eliminate the confounding effect of multiple exposures within the same household, 27 households with more than one primary case were excluded from analysis. Seven households in which no member took erythromycin were also excluded.

Of the remaining 37 households in which a single primary case of pertussis occurred and at least one member took erythromycin, 20 (with 93 members) had no additional cases. The remaining 17 households (with 96 members) had a total of 17 primary cases and 29 secondary cases. The median duration of cough in these 66 patients was 30 days. The age-specific attack rates of pertussis in the 37 households with a single primary case are shown in Table 1; 27 (41%) of 66 cases occurred in persons aged 7 years or older. Of the eight households in which patients with secondary disease were younger than age 1 year, five (63%) had patients with primary disease who were aged 7 years or older.

Risk Factors for Transmission

To identify risk factors for secondary transmission of pertussis following the onset of illness in the primary case, we compared the characteristics of the 17 households with secondary transmission to those of the 20 households without secondary transmission (Table 2). There were no significant differences in age distribution

Table 2.—Comparison of Characteristics Between Households (HHs) With and Without Secondary Spread of Pertussis

Characteristic	HH Group No Secondary Spread (n=20)	 Secondary Spread (n=17)
Median age (range), y	13.8 (<1-88)	10.0 (<1-58)
Male %	48	48
Median No. (range) of HH members	4 (2-9)	5 (2-12)
Crowding, % of HHs*	30	41
Income <$10 000 per y, % of HHs†	18	19
Race, % of HHs		
White, non-Hispanic	60	47
Hispanic	20	41
Private source of children's health care, % of HHs	53	82
Private source of children's vaccinations, % of HHs	37	47
% of contacts aged 7 mo to 18 y with ≥3DTP doses‡	86	81
Median age (range) of patients with primary cases, y	3.8 (<1-85)	6.8 (<1-39)
% of patients with primary cases aged 7 mo to 18 y with ≥3 DTP doses§	73	63
Culture-confirmed cases, %‖	40	20
% of patients with primary cases receiving medical care	100	82
% of all patients receiving medical care‖	100	78¶
Median interval (range) between onset of primary case cough and interview, d	61 (12-122)	62 (27-141)
Home visit interview, % of HHs	15	12

*Crowding is defined as more than 1.01 persons per room.

†The income level was known for 17 (85%) of 20 HHs with no pertussis spread, and 16 (94%) of 17 HHs with secondary spread.

‡DTP indicates diptheria and tetanus toxoids and pertussis vaccine. Vaccination status was known for 21 (51%) of 41 persons in HHs with no spread and 31 (61%) of 51 persons in HHs with secondary spread.

§Vaccination status was known for 11 (85%) of 13 persons in HHs with no spread and 8 (80%) of 10 HHs with secondary spread.

‖Includes primary and secondary cases.

¶$P=.03$ with two-tailed Fisher's Exact Test. No other differences were statistically significant.

Table 3.—Use of Erythromycin in Households (HHs) With Pertussis Disease

Erythromycin Status	HH Group No Secondary Spread (n=20)	 Secondary Spread (n=17)	*P*
Treatment of patients with primary case			
No. (%) treated with erythromycin	20 (100)	13 (76)	.04*
No. (%) treated within 3 wk of onset	16 (84)†	8 (62)	NS‡
Median duration (range) of treatment, d	14 (7-30)	14 (9-35)	NS
Median interval (range) to treatment, d§	11 (1-48)	21 (6-53)	.057‖
Prophylaxis for HH contacts			
No. (%) receiving prophylaxis	29/71¶ (41)	45/79 (57)	NS
No. (%) receiving prophylaxis within 3 wk of onset in patient with primary case	28 (97)	21 (47)	.00003#
Median duration (range) of prophylaxis, d	14 (10-21)	14 (10-38)	NS
Median interval (range) to prophylaxis, d§	16 (6-30)	22 (2-60)	.0008‖

*Two-tailed Fisher's Exact Test.

†The date that erythromycin treatment was begun was known for 19 (95%) of 20 patients.

‡NS indicates not significant.

§Interval from cough onset in patients with primary cases to initiation of treatment or initiation of prophylaxis in HH contacts.

‖Two-tailed Wilcoxon's rank sum test.

¶Two contacts with incomplete information on erythromycin use were excluded.

#Yates' continuity-corrected χ^2 analysis.

of household members, household size, crowding, income, race, source of children's health care or immunizations, or the proportion of contacts aged 7 months to 18 years who had received three or more doses of DTP. There were also no significant differences between the two household groups in the age distribution of patients with primary cases, vaccination status of patients with primary cases, proportion of culture-confirmed cases, proportion of patients with primary cases who received medical attention for their illness, or time from cough onset in primary cases to the interview date.

We then evaluated erythromycin treatment for patients with primary cases in the two groups of households (Table 3). More patients with primary cases in households with no secondary spread received erythromycin treatment compared with those in households with secondary spread (100% vs 76%; $P=.04$; two-tailed Fisher's Exact Test). There was also a significant delay in initiating therapy in the 17 households with secondary spread; in these households, a median of 21 days had elapsed between cough onset in the patient with the primary case and initiation of erythromycin treatment compared with 11 days in households with no secondary spread ($P=.057$; two-tailed Wilcoxon's rank sum test) (Table 3).

A similar analysis was done examining erythromycin chemoprophylaxis for household contacts. As shown in Table 3, there were no significant differences in the proportion of household contacts who received erythromycin prophylaxis or in the duration of prophylaxis. However, the median interval between cough onset in the patient with the primary case and initiation of erythromycin prophylaxis among contacts was significantly longer in households with secondary cases (22 days vs 16 days in households with no secondary transmission ($P=.0008$; two-tailed Wilcoxon's rank sum test) (Table 3).

Although households did not differ significantly in the proportion of patients with primary cases who sought medical care for their illness, there were eight households with secondary spread in which a patient with a primary case began erythromycin treatment either at the same time as or after a patient with a secondary case in the same household, suggesting that the patient with the secondary case may have brought the family to medical attention. Because this circumstance could have artificially lengthened the observed delay in initiating erythromycin treatment or prophylaxis, we repeated the analysis excluding these eight households. The net effect was that the median interval from cough onset in the patient with the primary case to initiation of treatment remained prolonged (21 days), and the median interval to initiation of prophylaxis became even more exaggerated (43 days) in households with secondary spread.

COMMENT

This outbreak, which is generally typical of those reported in the United States in recent years, involved a relatively high proportion of patients (40%) too old to be eligible for vaccination with the currently available whole cell pertussis vaccine. In addition, in our study, four of six patients younger than age 6 months with secondary cases, who were too young to have received the minimum number of DTP doses considered to provide adequate protection, resided in households in which the patient with the primary case was aged 7 years or older. Susceptibility of older children and adults to infection with *B pertussis* and their role in its transmission to younger, susceptible persons have been documented elsewhere.[13-16] These findings underscore the need to consider alternative control measures, such as the use of erythromycin when confronted with an outbreak of pertussis, particularly in view of high secondary attack rates (80% to 100%) among susceptible contacts.[3,5,6,17,18]

While there are no data from controlled clinical trials demonstrating that prompt initiation of erythromycin treatment in the patient with a primary case will result in decreased transmission to close contacts, the efficacy of this measure is supported by observational data from our study and others. Steketee et al,[17] in an institutional setting, found that infected persons with cough symptoms had shorter cough duration if treated with erythromycin within 1 week of illness onset, consistent with the findings of other studies.[11,13,19,20] Biellik et al,[10,21] in two separate investigations, found a delay in initiating erythromycin treatment among patients with primary cases in households with secondary transmission. In their studies, as well as ours, the occurrence of secondary cases in some households could not otherwise be explained by differences in susceptibility, such as age or vaccination status compared with households with no secondary spread. These data, combined with the results of microbiologic studies that have documented the effectiveness of erythromycin in eradicating nasopharyngeal carriage,[12] support the early use of this antimicrobial as standard therapy for pertussis. Although 5 days of therapy will reliably eradicate the organism, relapses or persistence of positive cultures have been reported after as many as 10 days of therapy.[11,22-25] Therefore, 14 days of treatment has been recommended to further reduce the likelihood of relapse.[11,23,26]

Our findings provide additional evidence that erythromycin prophylaxis is also important in reducing the risk of illness among close contacts of patients with pertussis. Delays in initiating prophylaxis were consistently longer in households with secondary cases than in households with no secondary cases, even when promptness of erythromycin therapy in primary cases was taken into account. These findings are virtually identical to those reported by Biellik et al in household-based studies in Wisconsin[10] and Delaware,[21] in which chemoprophylaxis was shown to be effective in all age groups. Because erythromycin was also administered therapeutically in the majority of households in our study, it was not possible to distinguish the relative importance of treatment vs prophylaxis. Although no secondary cases occurred in the seven households in which none of the members took erythromycin, all but one of the primary cases occurred in children younger than age 2 years. One potential explanation for this observation is that mild or asymptomatic infection occurred in an adult member who transmitted the organism to such children secondarily.[6,15]

Pertussis remains an important cause of morbidity and mortality, and lack of a recommended vaccine for those individuals aged 7 years or older may increase the likelihood of infection among older persons as well as the opportunity for transmission to those too young to be protected by vaccination. Data from controlled clinical trials demonstrating the effectiveness of erythromycin treatment and prophylaxis in limiting household spread are lacking.

Nevertheless, our results provide further evidence that erythromycin therapy and prophylaxis are effective and should be initiated promptly and often on an empiric basis, without awaiting relatively insensitive culture confirmation.[27] This recommendation should be emphasized particularly during outbreaks, when the occurrence of severe, paroxysmal cough is likely to represent true pertussis disease, and in households and other settings in which unvaccinated or inadequately vaccinated persons (ie, those individuals younger than age 7 months or those with contraindications to vaccination[7,8]) are at increased risk of contracting the disease.

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Vitamin A Levels and Severity of Measles

New York City

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• Recent studies show that vitamin A levels decrease during measles and that vitamin A therapy can improve measles outcome in children in the developing world. Vitamin A levels of children with measles have not been studied in developed countries. We therefore measured vitamin A levels in 89 children with measles younger than 2 years and in a reference group in New York City, NY. Vitamin A levels in children with measles ranged from 0.42 to 3.0 μmol/L; 20 (22%) were low. Children with low levels were more likely to have fever at a temperature of 40°C or higher (68% vs 44%), to have fever for 7 days or more (54% vs 23%), and to be hospitalized (55% vs 30%). Children with low vitamin A levels had lower measles-specific antibody levels. No child in the reference group had a low vitamin A level. Our data show that many children younger than 2 years in New York City have low vitamin A levels when ill with measles, and that such children seem to have lower measles-specific antibody levels and increased morbidity. Clinicians may wish to consider vitamin A therapy for children younger than 2 years with severe measles. Additional studies of vitamin A in measles and other infectious diseases, and in vaccine efficacy trials, should be done.

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In developing countries, measles is a leading cause of mortality, accounting for 1.5 million childhood deaths each year.[1] In the United States in 1990, there were more than 25 000 cases and more than 90 deaths from measles.[2] Immunization is the primary means of preventing measles mortality, but high infectivity, incomplete vaccine coverage, and vaccine failures highlight the need for effective therapy. Recent studies suggest that vitamin A is one such therapy.

It has been shown that vitamin A levels decrease during measles infection,[3,4] and that low levels are associated with increased measles mortality.[5] Clinicians in developing countries have long recognized that xerophthalmia commonly follows measles, and measles is the precipitating cause of as much as half of childhood blindness in parts of Africa.[6,7] One trial of vitamin A therapy for measles in 1932[8] and two recent randomized, placebo-controlled trials have shown improved outcome in children younger than 2 years[9,10]; none of the children studied had clinical vitamin A deficiency. The authors of one of these studies[10] suggested that infection may reduce vitamin A levels in children whose levels are usually normal and that vitamin A therapy is indicated for "all children seriously ill with measles."

The World Health Organization recommends vitamin A therapy for children with measles who live in communities with known vitamin A deficiency and in communities where the measles case-fatality ratio is 1% or greater.[11] These recent studies suggest that this recommendation may need to be extended to all children younger than 2 years with severe measles.

Whether children in developed countries with measles may benefit from vitamin A therapy is unknown. We, therefore, conducted a study to determine whether vitamin A levels in children with measles in New York City are low, and, if so, whether low levels correlate with more severe measles. We also analyzed the relationship between vitamin A levels and measles-specific antibody production. Because vitamin A levels in healthy children younger than 2 years have not been studied in the United States, a reference group of children without acute illness was also analyzed.

SUBJECTS AND METHODS

All children younger than 2 years reported to the New York City Department of Health with confirmed measles during the 18-month period January 1, 1989, through June 30, 1990 (study period), were eligible for enrollment. Measles was defined as illness with fever above 38.3°C, rash for more than 2 days, and one of the following: cough, conjunctivitis, or coryza, plus serological confirmation of acute infection or epidemiological linkage to a serologically confirmed case. As part of New York City's surveillance system, public health personnel completed standardized forms containing clinical and epidemiological information obtained from hospital records, physicians, parents, and other primary caretakers of children with measles. This information included age, gender, ethnicity, vaccination status, measles onset, hospitalization, pneumonia, diarrhea, duration of rash, duration of fever, and maximum fever. Income was estimated using zip code–specific median household income from the 1980 census. Physicians were asked to confirm the diagnosis of measles serologically. Vitamin A therapy was not given to children with measles.

To evaluate vitamin A levels in children without acute illness, plasma samples from a reference population of 60 children younger than 2 years being screened for elevated serum lead levels were obtained from the Lead Unit, New York City Department of Health. These specimens were submitted from child health stations, municipal clinics and hospitals, and private

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practitioners. Specimens drawn to confirm elevated lead levels were excluded.

Specimens were retrieved from the Bureau of Laboratories, New York City Department of Health, where they had been protected from light and stored at −20°C. Plasma was centrifuged to remove fibrin. Serum or plasma was denatured with an equal volume of ethanol containing an internal standard. Hexane was added, the specimen was vortex mixed, and the phases were separated by centrifugation. The hexane layer was removed and evaporated to dryness. The extract was reconstituted with ethanol and the extracts were filtered and placed in a refrigerated autosampler. The extracts were analyzed by reverse-phase high-performance liquid chromatography as follows: 30 µL of extract was injected onto an octadecylsilane column (Phenomenex Ultramex 5µ, 4.6 mm × 15 cm, Phenomenex, Torrance, Calif) with a mobile phase consisting of 1:1 ethanol:acetonitrile at a flow rate of 0.9 mL/min. The detector (Waters Model 490, Waters Chromatography Division, Marlboro, Mass) detected vitamin A at 325 nm. Total measles-specific hemagglutination-inhibition antibody titers were measured using purchased antigen (Whitaker Microbiological Associates, Walkersville, Md), then non-IgM antibody was adsorbed using protein A (Calbiochem-Behring Corp, La Jolla, Calif), and IgM titers were measured. The lowest dilution detectable was 1:10.

Vitamin A levels, determined from remnant serology serum samples, were considered low if they were less than 0.70 µmol/L[12] and borderline if they were 0.70 to 0.87 µmol/L. Differences in measles severity were compared for children with low and normal (including borderline) vitamin A levels using the Mantel-Haenszel χ^2; when an expected value was less than 5, Fisher's Exact Test (two-tailed) was used. To compare continuous data, Student's *t* test was used for normally distributed data; otherwise, the Wilcoxon Two-Sample Test was used. Pearson correlation coefficients were calculated using the $\log_2$ of the antibody titer, and analyses of antibody titers were done using the geometric mean titer. To evaluate the effect of vitamin A level and interval between rash onset and vitamin A measurement on antibody levels, analysis was stratified by week of phlebotomy. Statistical tests were done using Epi Info, Version 5.[13] All specimens were taken from serum samples that would otherwise have been discarded, and all identifiers were removed before analyses was done.

RESULTS

Measles Cases

During the 18-month study period, 224 confirmed cases of measles in New York City in children younger than 2 years were reported. Of the 167 serologically confirmed cases, serum was available from 89. Of the 89 children studied, 68 (76%) were Hispanic and 17 (19%) were non-Hispanic black. Mean age was 12 months (range, 2 to 23 months). Only six children had a documented history of measles vaccination. Among the 135 children with confirmed measles whose serum samples were unavailable, all demographic and clinical characteristics except hospitalization rate were similar (Table 1). The higher proportion of children hospitalized in the group of children with measles not studied likely represents children whose serological analysis had been done by a local hospital and whose serum was thus unavailable for this study.

Vitamin A Levels

Vitamin A levels measured in serum drawn for acute-phase serological tests for measles ranged from 0.42 to 3.0 µmol/L (mean, 1.1 µmol/L). Twenty children (22%) had low levels (<0.70 µmol/L), and an additional 23 (26%) had borderline levels (0.70 to 0.87 µmol/L). Specimens obtained for acute-phase serological study were drawn a median of 5 days after rash onset (range, 1 to 37 days).

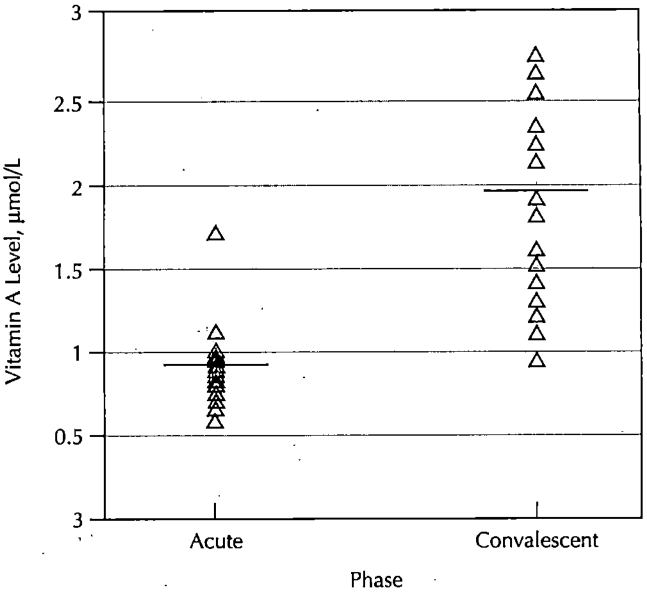

Fig 1.—*Vitamin A levels in paired measles serological specimens (bars indicate mean levels). Of the 89 children studied, 21 had paired serum samples available. All paired serum specimens but one showed an increase in vitamin A level from first to second specimen.*

Vitamin A level correlated with interval between rash onset and vitamin A measurement, with levels drawn later in the course of measles being higher than those drawn earlier ($P<.01$). For 21 children, both acute-phase serum samples (drawn a median of 5 days after rash onset) and convalescent-phase serum samples (drawn a median of 19 days after rash onset) were available. For these children, the mean vitamin A level in acute-phase serum was 0.92 µmol/L (range, 0.59 to 1.7 µmol/L) and more than doubled to 1.9 µmol/L (range, 0.94 to 2.7 µmol/L) in convalescent-phase serum (paired two-tailed *t* test, $P<.001$; Fig 1). All paired serum specimens but one showed an increase in vitamin A level from first to second specimen.

Vitamin A levels were similar by household income, age, and gender of child (Table 2). The six children who had been vaccinated were similar to the 83 nonvaccinated children in measles severity and vitamin A levels (mean vitamin A level, 0.92 µmol/L).

Reference Group

Like the children with measles, reference children were drawn primarily from municipal institutions. Median household income in zip codes of children in the reference group was $9985, which was similar to that of study children. Of the 60 reference children, 72% were male, 52% were black, 38% Hispanic, 7% Asian, and 3% white. Mean age was 15 months. Vitamin A levels ranged from 0.70 to 2.1 µmol/L (mean, 1.3 µmol/L). Levels were similar by age, gender, and ethnicity. No specimen had a low vitamin A level, and median vitamin A levels were higher than those of children with measles for the entire group ($P<.001$), and for every age, gender, and ethnic subgroup.

Vitamin A and Severity of Measles

Of the 89 children with measles, 32 (36%) were hospitalized, 33 (37%) had diarrhea (duration unknown), and nine (10%) had pneumonia. Mean duration of rash and fever were 6.1 and 5.1 days, respectively (ranges, 3 to 14

Table 1.—Characteristics of Children Younger Than 2 Years With Reported Confirmed Measles

	Study Group (n=89)	All Others (n=135)
Mean age, mo	12.1	11.7
Rash duration, mean d	6.1	6.3
Days hospitalized, mean	5.4	6.3
Median household income, $	9721	9985
% F	51	48
Race, %		
Hispanic	76	70
Non-Hispanic black	19	21
Non-Hispanic white	1	6
Asian	3	3
Vaccinated, %	7	6
Hospitalized, %	36	54*
Pneumonia, %	10	16
Diarrhea, %	37	41

*$P=.008$.

Table 2.—Demographic Characteristics and Vitamin A Levels in Children Younger Than 2 Years With Confirmed Measles

		Vitamin A Level, No. (%)	
	No.	Low (<0.70 μmol/L)	Borderline (0.70-0.87 μmol/L)
Age, mo			
<6	7	3 (43)	2 (29)
6-11	40	8 (20)	12 (30)
12-17	28	4 (14)	5 (18)
18-23	14	5 (36)	4 (29)
Sex			
M	44	9 (20)	10 (23)
F	45	11 (24)	13 (29)
Race			
Hispanic	68	17 (25)	18 (26)
Non-Hispanic black	17	3 (18)	5 (29)
Non-Hispanic white	3	0 (0)	0 (0)
Non-Hispanic Asian	1	0 (0)	0 (0)
Total	**89**	**20 (22)**	**23 (26)**

and 1 to 14 days). Mean maximal temperature, which was recorded for 85 children, was 39.7°C. Among the 32 patients who were hospitalized, mean length of stay was 5.4 days (range, 1 to 10 days). Indicators of measles severity were similar by household income, age, ethnicity, and gender with the exception of diarrhea, which was more common in younger children ($P=.02$). None of the 224 children with confirmed measles died.

Analysis of measles severity related to vitamin A levels showed that children with low vitamin A levels were more likely to have fever at a temperature of 40°C or higher (68% vs 44%; $P=.06$) and to have fever for more than 7 days (54% vs 23%; $P=.04$). Children with low levels were more likely to be hospitalized (55% vs 30%; $P=.05$; Table 3). This difference was also apparent for children with borderline vitamin A levels (χ^2 for linear trend, 5.124; $P=.02$). Median vitamin A levels were 0.84 μmol/L in hospitalized children, compared with 0.98 μmol/L in nonhospitalized children ($P=.02$). This difference was not due to the hospitalization itself, since levels were similar in those children whose vitamin A level was measured on admission and those whose vitamin A level was measured later in the hospital course. Stratification by age group, gender, and week of vitamin A collection in the course of illness did not substantially alter the association of low vitamin A levels with increased fever or hospitalization rate. Even among children not hospitalized, those with low vitamin A levels were more likely to have fever at a temperature of 40°C or higher (78% vs 65%; $P=.03$).

Vitamin A Levels and Measles-Specific Antibodies

Children with low vitamin A levels were more likely to have low measles-specific antibody titers (19 of 20 vs 37 of 69; $P<.001$), as defined by a total measles-specific antibody titer less than 1:80 (four dilutions). Similarly, children with low measles-specific antibody titers had lower vitamin A levels than children with high measles-specific antibody titers (0.94 vs 1.45 μmol/L; $P=.001$).

To control for the effect of timing of measurement on vitamin A and antibody levels, we stratified according to week of phlebotomy. In this analysis, vitamin A levels measured at least 1 week after rash onset, but not those measured during the first week, were associated with antibody titers (Fig 2). Children with low vitamin A levels whose blood was drawn after the first week of illness had lower geometric mean measles-specific antibody titers (1:20 vs 1:80; $P=.002$) and were more likely to have a low antibody level (7/7 vs 13/37; $P=.002$). In addition, children in this group with low antibody titers had lower vitamin A levels (1.03 vs 1.83 μmol/L; $P<.001$). These results are similar when the six vaccinated children are excluded from the analysis.

Table 3.—Indices of Severity of Measles by Vitamin A Level

	Vitamin A Level		
	Low (<0.70 μmol/L) (n=20)	Normal (0.70 μmol/L)* (n=69)	*P*
Highest temperature (mean), °C	40	39.6	.02
Fever duration, mean d	6.2	4.8	.04
Rash duration, mean d	6.1	6.0	.87
Fever ≥7 d, %	54	23	.04
Temperature at ≥40°C, %	68	44	.06
Hospitalized, %	55	30	.05
Diarrhea, %	35	36	.92
Pneumonia, %	10	10	1.00

*Includes borderline (0.70 to 0.87 μmol/L).

COMMENT

Clinical vitamin A deficiency is almost unknown in New York City, and none of the children in the reference group had low levels. Nevertheless, nearly one in four children with measles in New York City had low levels of vitamin A, and almost half had either low or borderline levels. Children with low vitamin A levels seemed to have more severe measles, as evidenced by longer and higher fever and increased hospitalization rate. We postulate

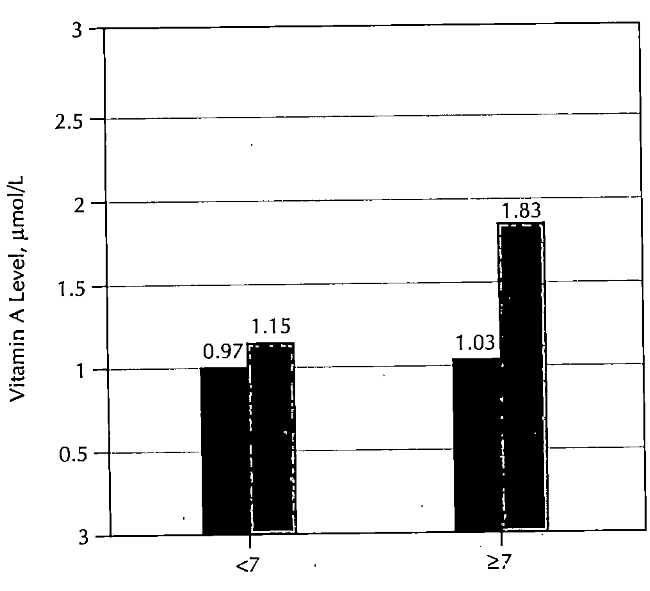

Fig 2.—*Vitamin A levels in children with measles, by antibody titer (solid bars, <1:80; shaded bars, ≥1:80) and time of measurement. Children with low vitamin A levels after the first week of illness were more likely to have low antibody titers (less than four dilutions). Comparison of vitamin A levels of children whose levels were measured within 7 days of rash onset,* P=*.58; at 7 days or greater,* P<*.001.*

that measles virus infection lowers vitamin A levels and that low vitamin A levels in turn exacerbate measles severity, possibly by reducing antibody production.

Although vitamin A levels are low in infections other than measles,[14-16] only for measles has the relation between vitamin A and severity been studied. Vitamin A levels are stable for months in healthy adult volunteers fed a vitamin A-deficient diet[17]; low levels during infection do not result from reduced intake. The mechanism of this decline is unknown, but may be reduced mobilization[18] due to low zinc,[19] prealbumin,[20] or retinol-binding protein levels.[3,21]

Although we found that circulating vitamin A levels were normal during convalescence, total body stores of vitamin A may be depressed for months after measles infection. Campos et al[14] reported that after an episode of chickenpox, children had inadequate total body reserves of vitamin A for 3 months or longer despite normal circulating levels. In developing countries, children who survive measles have increased morbidity[22,23] and mortality[24,25] from respiratory infections and diarrhea for at least 1 year. Since vitamin A deficiency increases the severity of bacterial, viral, and parasitic infections,[26] and is associated with increased diarrheal and respiratory morbidity[27,28] and mortality,[29] the decline in total body stores of vitamin A caused by measles may contribute to increased postmeasles mortality. Thus, vitamin A therapy for measles could reduce both short- and long-term postmeasles mortality. This effect could account for some of the reduction in mortality seen in community-wide vitamin A supplementation trials.[30]

Our finding of an increased risk of fever and hospitalization in children with low levels of vitamin A, although not dramatic, is consistent with other studies that have shown more severe measles in children with low vitamin A levels. However, hospitalization may reflect social and economic factors in addition to measles severity. Hussey and Klein[10] found that vitamin A therapy shortened duration of pneumonia and diarrhea and reduced measles mortality. In the current series, information about duration of pneumonia and diarrhea was unavailable, and there were no deaths. Therefore, we could not evaluate the indicators of measles severity that may be most affected by low vitamin A levels.

The mechanism by which vitamin A depletion exacerbates infection is unknown. In experimental models, vitamin A deficiency impairs cellular immunity,[31] delayed-type hypersensitivity,[32] and antibody production.[33,34] Vitamin A supplementation improves phagocytic function of cultured human macrophages.[35,36] In animal models, vitamin A depletion leads to marked atrophy of the thymus and spleen,[37,38] and vitamin A deficiency has been associated with impaired antibody production.[39,40] Decreased levels of measles antibodies have been associated with increased measles mortality.[41]

Improvement in antibody production may explain the efficacy of vitamin A therapy in the treatment of measles. Pasatiempo et al[39] studied the effect of vitamin A depletion on antibody production in rats challenged with a capsular polysaccharide antigen of *Streptococcus pneumonia*. They found that antibody response was reduced by nearly 80% in vitamin A–deficient rats, but that vitamin A supplementation as late as 1 day after antigenic challenge increased antibody response to near that of rats without vitamin A deficiency. The correlation between vitamin A levels and measles-specific antibodies in the current study suggests that low vitamin A levels may exacerbate infection by reducing antibody production. Alternatively, protein malnutrition may have caused both low antibody levels (by limiting synthesis) and low vitamin A levels (by reducing binding proteins). The relation between vitamin A and antibody production suggests that the effect of vitamin A supplementation on vaccine efficacy should be investigated.

Our study population consisted of children younger than 2 years, most of whom were black or Hispanic. We chose to study only children younger than 2 years because vitamin A levels are most labile in young children[18] and because low serum vitamin A levels have been associated with increased measles mortality in children younger than 2 years.[5] In addition, controlled trials of vitamin A therapy reduced measles mortality only in children younger than 2 years.[8-10] Serum samples from children with measles had been frozen for up to 18 months; vitamin A levels have been shown to be stable in frozen samples for several years.[42] Vitamin A levels of reference children were measured in plasma as opposed to serum samples. However, plasma and serum specimens yield similar results,[43] and any discrepancy would not alter our findings in children with measles.

Vitamin A levels are low in developing countries. This study reveals that levels are also low in many young children with measles in New York City. In our study, children with low vitamin A levels seemed to have more severe measles. This study cannot establish whether low vitamin A levels cause or result from severe measles; however, the finding in other studies that vitamin A therapy improves measles outcome strongly suggests that vitamin A deficiency exacerbates measles infection.

Vitamin A is inexpensive, and single or split doses of 100 000 to 400 000 IU (depending on weight) are relatively safe. Multiple or higher doses may cause rash and severe neurological symptoms and should not be given. Vitamin A has been recommended for children with severe measles in developing countries. Clinicians may wish to consider vitamin A therapy for children younger than 2 years with severe measles in the United States as well. Additional studies of vitamin A in measles, other infectious diseases, and vaccine efficacy trials should be done.

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Failure of Thrombolytic Therapy in Four Children With Extensive Thromboses

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• In three children with central vein thromboses and a fourth with a pulmonary artery thrombosis, thrombolytic therapy failed to produce ultrasonographic evidence of clot lysis. Low-dose streptokinase (50 to 250 U/kg per hour) was infused directly into the clot in three children, followed by streptokinase and urokinase in systemic doses (streptokinase, 1000 to 1750 U/kg per hour; urokinase, 4400 to 5000 U/kg per hour). A fourth child treated sequentially with systemic doses of streptokinase, urokinase, and recombinant tissue-type plasminogen activator developed a significant retroperitoneal and intrapleural hemorrhage after 19 hours of recombinant tissue-type plasminogen activator infusion at a dose of 0.7 mg/kg per hour. All of the children survived. The most likely reason for treatment failure was that the clots (estimated to be between 2 and 3 weeks of age) were organized and thus resistant to lysis. Early diagnosis and prompt thrombolysis of significant lesions may contribute to the successful management of pediatric thrombosis. However, controlled studies are clearly needed to establish guidelines for the optimal use of thrombolytic agents in children.

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A number of case reports have documented the success of streptokinase and urokinase in the dissolution of intracardiac, venous,[1-10] and arterial[11-16] clots in infants and children. Thrombosis of pulmonary arteries,[17] prosthetic valves,[18] and pulmonary artery grafts[2,19] have also been successfully treated with thrombolysis. More recently, successful management of a pulmonary embolus[20] and lysis of arterial and venous clots[21,22] in children have been reported with the use of recombinant tissue-type plasminogen activator.

In contrast, failure of thrombolytic agents to lyse arterial[23-25] and pulmonary artery[26] clots have rarely been reported. In a series of 12 catheter-related venous thrombi treated with urokinase, Curnow et al[3] reported only one therapy failure. These reports, which, to our knowledge, include all English-language reports on pediatric use of thrombolytics, are summarized in Table 1. The use of thrombolytics to achieve catheter patency in occluded central lines was not included.

Since no controlled investigations have been reported on the use of thrombolytics in children, the preponderance of successful outcomes over treatment failures may give a false impression of the efficacy of such agents. It is important, therefore, that therapy failures, in addition to successes, should continue to be examined if appropriate conclusions are to be drawn as to the indications and efficacy of thrombolytic therapy.

We describe the courses of three children with central vein thromboses and a fourth with pulmonary artery thrombosis, all of which were resistant to thrombolytic therapy, including recombinant tissue-type plasminogen activator in one case. The possible reasons for failure of thrombolytic therapy are discussed.

PATIENT REPORT

PATIENT 1. —A male infant was examined at 3 weeks of age with a 24-hour history of cyanosis of the lower extremities and lower part of the abdomen. A right femoral venacavogram showed complete occlusion of the inferior vena cava (IVC) up to the hepatic segment in addition to occlusion of the left femoral vein, with filling only of the azygous system. Blood flow was present in the renal veins by ultrasound Doppler studies.

The femoral catheter vein was left in situ, embedded into the thrombus, and low-dose streptokinase was infused into the catheter (Table 2). Heparin (20 U/kg per hour) was administered concomitantly, along with daily infusions of plasma (10 mL/kg per day) for 5 days. After 48 hours of low-dose streptokinase therapy, there was no clinical improvement and no change in the clot size on ultrasound examination. Streptokinase was increased to systemic doses (1000 to 1200 U/kg per hour) after a loading dose of 10 000 U/kg, and the heparin infusion was discontinued. Twenty-four hours later, there was a marked clinical improvement in the edema and cyanosis of the lower limb; however, the clot still extended from the hepatic section of the IVC to the level of the renal veins on ultrasound examination. Systemic urokinase (4400 to 5000 U/kg per hour) was infused after a bolus dose for a further 72 hours without sonographic resolution of the clot. Fibrinogen levels during systemic thrombolytic therapy were always less than 2 g/L, the lowest fibrinogen level achieved being 1.43 g/L.

Results of investigations on admission included a low antithrombin III level; however, the antithrombin III level tested again during the convalescent period was normal (Table 3). Protein C and protein S levels were within normal limits for age.[27] The values in the patient's parents were also normal.

The infant was given anticoagulation treatment with warfarin

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Table 1.—Review of the Pediatric

Source, y	Patient Age	Site	Maximum Age of Clot	Agent	Bolus
Bhat et al,[23] 1981	9 d	Aorta	9 d	UK	–
Delaphane et al,[1] 1982	15 wk	RA	3 mo	UK	+
Rao et al,[11] 1982	12 d	Aorta	12 d	UK	+
	3 d	Aorta	3 d	UK	+
	7 d	R femoral artery	6 d	UK	N/A
	2 d	Brachial	1 d	UK	N/A
Corrigan,[24] 1982	11 d	Aorta	N/A	UK	+
Hassal et al,[26] 1983	3½ y	RA	4 mo	UK	N/A
Joyce et al,[18] 1983	16 mo	Prosthetic tricuspid valve	N/A	UK	+
Beaufils et al,[17] 1985	10 y	Pulmonary artery	N/A	UK	+
				UK	+
	7 y	Pulmonary artery	N/A	UK	12 500 (bolus ×2)
				UK	15 000 (bolus ×1)
Curnow et al,[3] 1985	11 children, 6 wk–43 mo	Central veins (10), RA (1)	N/A	UK	+
Olsen et al,[5] 1985	20 mo	RA	2 wk	SK	+
Pritchard et al,[2] 1985	1 mo	Aorta	1 mo	SK	–
	4 mo	P-S	1 d	SK	–
	4 d	IVC, renal veins	7 d	SK	–
LeBlanc et al,[19] 1986	11 d	Aorta	11 d	SK	–
	11 y	Renal artery shunt	N/A	SK	–
	18 mo	B-T shunt	N/A	SK	–
	10 d	Aorta	10 d	SK	–
	1 d	Aorta	1 d	SK	–
				UK	–
Pongiglione et al,[6] 1986	1 mo	RA	17 d	UK	–
	21 d	RA	13 d	UK	–
Zureikat et al,[7] 1986	9 wk	RA	21 d	UK	+
Vailas et al,[16] 1986	8 infants, 2-35 d	Aorta (3; moderate thrombosis),	2-35 d	SK	+
		aorta (5; severe thrombosis)		SK or UK	+
Emami et al,[25] 1987	7 d	Aorta	7 d	SK	+
				UK	+
Marsh et al,[10] 1988	9 d	RA (after ECMO)	4 d	UK	N/A
	1 mo	RA (after ECMO)	9 d	UK	N/A
Griffin and Casta,[4] 1988	21 d	SVC	14 d	UK	+
Kirk et al,[12] 1988	2 d	Aorta	24 h	SK	+
Strife et al,[13] 1988	8 infants, 1-16 d	Aorta (6), peripheral artery (2)	1-16 d	SK (3)	+
				UK (4),	+
				SK+UK (1	
Vogelzang et al,[9] 1988	9 y	Renal vein	N/A	UK	–
Goldberg et al,[14] 1989	6 d	Aorta	6 d	SK	N/A
		IVC	. . .	UK	+
Reznik et al,[15] 1989	15 d	Aorta	13 d	UK	–
Suarez et al,[8] 1989	6 wk	RA	27 d	UK	+
Kennedy et al,[21] 1990	4 d	Aorta	4 d	rt-PA	–
Pyles et al,[20] 1990	19 mo	Pulmonary artery	N/A	rt-PA	–
Levy et al,[22] 1991	11 children, 1 d–17 y	Iliac artery (1),	N/A	SK	N/A
		peripheral artery (7),		UK	N/A
		central vein (3)		rt-PA	–

*UK indicates urokinase; SK, streptokinase; rt-PA, recombinant tissue-type plasminogen activator; RA, right atrium; P-S, pulmonary to systemic; SVC, superior vena cava; IVC, inferior vena cava; N/A, not applicable or not available; IVH, intraventricular hemorrhage; ARF, acute renal failure; B-T, Blalock-Taussig; and ECMO, extracorporeal membrane oxygenation. Maximum age of clot was determined from the time of insertion of the catheter to the diagnosis of clot.

Literature on Thrombolytic Therapy*

Thrombolytic Dose Range, U/kg per h	Duration	Concomitant Heparin	Outcome	Subsequent Anticoagulation
4000	24 h	No	No lysis → thrombectomy	None
4400-8000	10 h	Yes	Recurrence of clot; UK (52 800 u/kg per h) repeated for 12 h → lysis	Heparin
2000	36 h	No	No lysis → thrombectomy	None
2000	6 d	Yes	Lysis	Heparin
N/A	12 h	No	Lysis	None
N/A	12 h	No	Lysis	None
8800	12 h	No	No lysis; a ARF → death	N/A
N/A	4 h	No	Pulmonary embolus	None
5000-10 000	40 h	No	Lysis	Heparin/warfarin
3000	3 d	Yes	Recurrence of thrombus, partial lysis	Heparin/warfarin
4500	4 d	Yes		
. . .	. . .	No	Partial lysis	Heparin/warfarin
. . .	. . .	No		
4400-8800	4 h	No	Lysis in 11/12 episodes	Heparin lock to catheters
4400	16 h	No	Lysis	None
50	44 h	No	Near-complete lysis	Heparin/warfarin
150	48 h	No	Shunt patent	Warfarin/aspirin
50	72 h	Yes	Significant lysis	Heparin/warfarin
50-100	11 d	No	Lysis	Heparin/warfarin
50	4 d	No	Lysis	N/A
50	4 d	Yes	Lysis	Heparin/warfarin
50	10 d	Yes	Lysis	Heparin/warfarin
50-100	5 d	Yes	No lysis	. . .
400	1 d		ARF → death	. . .
2000-3000	12 d	Yes	Lysis	None
2000-4500	10 d	Yes	Lysis	None
2000-8000	72 h	No	Lysis; developed pulmonary embolism (resolved)	None
3000	5-6 d	No	Lysis (2), thrombectomy (1)	None
N/A	N/A	No	Died (5)	N/A
12 500	12 h	No	No lysis; developed IVC clot during	Heparin
50 000	21 h	No		
N/A	2 d	No	No lysis → thrombectomy	None
N/A	1 d	No	Lysis	None
6000-8000	10 h	No	Lysis	Heparin
1000	30 h	No	Lysis	Heparin
400-1200	. . .	Yes	Lysis (5), partial lysis (3), IVH (2) → death (1)	Heparin
4000-20 000	48 h–9 d	4/6 infants		
50-120 000	42 h	No	Lysis	Warfarin
N/A	24 h	Yes	Lysis	Heparin/warfarin
4400	4 d	Yes		
10-16 000	9 d	No	Lysis	None
4400-6600	24 h	No	Lysis	None
0.47 mg/kg per h	3 h	No	Lysis	None
0.1 mg/kg per h	11 h	No	Lysis; repeat pulmonary embolus → death	N/A
N/A	N/A	No	6/11 lysis, 4/11 partial lysis, 6/11 bleeding	None
N/A	N/A	No		
0.1-0.5 mg/kg per h	2 h–3 d	No		

Table 2.—Patient Characteristics, Therapy, and Outcome*

	Patient			
	1	2	3	4
Age	3 wk	10 y	8 wk	5 wk
Thrombus location	L femoral, IVC, renal veins	R and L femoral, IVC, hepatic and renal veins, R subclavian	R pulmonary artery	IVC
Duration (approximate), wk	3	2	3	3
Cause	Unknown	Unknown	B-T shunt	*Candida* septicemia
Streptokinase				
Bolus, U/kg	. . .	1000	. . .	. . .
Dose, U/kg per h	50-125	1000-1750	50-125	100-250
Duration, h	72	48	72	96
Route	Intraclot	Intravenous	Intraclot	Intraclot
Bolus, U/kg	1000	. . .	1000	. . .
Dose, U/kg per h	1000-1750	. . .	1000-1750	. . .
Duration, h	48	. . .	48	. . .
Route	Intravenous	. . .	Intravenous	. . .
Urokinase				
Bolus, U/kg	4400	4400	4400	4400
Dose, U/kg per h	4400-5000	4400	4400-5000	4000-5000
Duration, h	120	16	120	72
Route	Intravenous	Intravenous	Intravenous	Intravenous
rt-PA				
Bolus, U/kg	Not given	. . .	Not given	Not given
Dose, U/kg per h	. . .	0.7	. . .	. . .
Duration, h	. . .	19	. . .	. . .
Route	. . .	Intravenous	. . .	. . .
Ancrod				
Dose, U/kg per h	Not given	0.04-0.2	Not given	Not given
Duration, d	. . .	7	. . .	. . .
Route	. . .	Intravenous	. . .	. . .
Complications of therapy	None	Retroperitoneal/pleural hemorrhage	None	None
Subsequent anticoagulation	Warfarin	Warfarin	Warfarin	None
Outcome	Clinical improvement, no lysis of thrombus	Clinical improvement, no lysis of thrombus	Clinical improvement, no lysis of thrombus	Clinical improvement, no lysis of thrombus

*IVC indicates inferior vena cava; B-T, Blalock-Taussig; and rt-PA, recombinant tissue-type plasminogen activator.

sodium. There was no extension or regression of the clot on ultrasound 9 months later, and the infant remained clinically well.

PATIENT 2.—A previously healthy 10-year-old girl presented with pain and swelling of her left leg. A venogram showed poor filling of the popliteal or femoral veins due to extensive clot formation. An ultrasound examination showed that the clot extended into the internal iliac to the junction of the IVC but did not involve the IVC at that time. The patient's mother and paternal grandmother had histories of phlebitis, while her identical twin sister was asymptomatic.

After 24 hours of a heparin infusion, streptokinase was instituted at systemic doses (Table 2). Forty-eight hours later, the pain in her thigh and calf had lessened, although the leg remained edematous. Streptokinase treatment was discontinued, and she was given heparin. One week later, she developed left flank pain and hematuria. An ultrasound examination showed that the thrombus now involved the IVC up to the level of the hepatic veins and down the right iliac vein. Both renal veins were occluded, and the kidneys were enlarged. Systemic urokinase treatment was initiated but was given only for 16 hours, since further supplies of the drug were unavailable. Treatment was therefore started with recombinant tissue-type plasminogen activator at a rate of 0.7 mg/kg per hour. There was no clinical or ultrasonographic improvement 4 hours later, and after 19 hours of recombinant tissue-type plasminogen activator infusion, the patient developed clinical signs of a retroperitoneal and left pleural hemorrhage, which was confirmed by a computed tomographic scan. The recombinant tissue-type plasminogen activator infusion was discontinued, and heparin was recommended along with warfarin.

Two days later, despite activated partial thromboplastin times between 50 and 70 seconds, the patient developed fresh pain, swelling, tenderness, and a positive Homan's sign in the right calf. Treatment was started with an infusion of the antifibrinogen agent ancrod, a derivative of the venom of the Malayan pit viper, and heparin treatment was discontinued. Fibrinogen levels were less than 0.15 g/L at one point during ancrod therapy, but they were generally maintained between 0.5 and 1 g/L.

To document the feasibility of surgical intervention and to exclude pulmonary embolization, a cardiac catheterization was performed via a right antecubital fossa vein. Confirmation of the clot within the IVC to the level of the hepatic veins was obtained; the pulmonary artery was patent, and pulmonary vascular resistance was normal. The catheter was left in the axillary vein because of difficulty with venous access. Five days later, while still receiving ancrod, the patient developed signs of an axillary vein thrombosis, confirmed by ultrasonography, which also showed the clot extending into the superior vena cava. The pain and swelling of the limb subsequently resolved during ancrod therapy on removal of the catheter and elevation of the arm. Ancrod treatment was discontinued 3 weeks later when a therapeutic prothrombin time was achieved with war-

Table 3.—Results of Investigations*

	Patient			
	1	2	3	4
Changes in coagulation factors during thrombolytic therapy				
Longest PT, s	20.6	17.1	20.6	13.2
Longest PTT, s	98.9	105	98.9	50.5
Lowest fibrinogen, g/L	1.43	0.96	0.82	1.25
Longest TT/control, s	19.5/9.3	19.5/9.3	N/A	N/A
FDPs, mg/mL				
Pretreatment	<10	<10	<10	<10
During treatment	>40	>40	>40	>40
AT III, U/mL	0.38 (L) (0.48-1.08); 0.86† (0.73-1.21)	0.98 (0.72-1.25)	0.63 (0.48-1.08)	0.65 (0.48-1.08)
Plasminogen mg/dL (pretreatment)	6.5 (L) (7.5-13.7)	4.9 (L) (7.5-13.7)	N/A	N/A
Protein C activity, U/mL	0.41 (N/A for infants)	0.87 (0.63-1.27)	0.57 (N/A for infants)	0.63 (N/A for infants)
Protein C antigen, U/mL	0.38 (0.21-0.65)	N/A	0.86 (0.21-0.65)	0.62 (0.21-0.65)
Protein S, U/mL				
Total	1.04 (0.33-0.93)	1.39 (0.72-1.4)	0.82 (0.33-0.93)	0.58 (0.33-0.93)
Free	0.4 (N/A for infants)	0.94 (0.66-1.5)	0.62 (N/A for infants)	0.62 (N/A for infants)
Ultrasound of head (posttherapy)	Normal	N/A	Normal	N/A

*Normal values are given in parentheses. PT indicates prothrombin time; PTT, partial thromboplastin time; TT, thrombin time; FDPs, fibrin degradation products; AT III, antithrombin III; N/A, not available; and L, low value.

†Repeated level during convalescence at 6 months of age.

farin. The patient had no further evidence of thrombosis while taking warfarin.

Results of investigations included normal antithrombin III, protein C, and protein S levels (Table 3). Normal levels of DNA antibodies (<0.03 U/L) and a negative fluorescent antinuclear antibody test did not support an autoimmune source for the thrombosis.

Patient 3.—A female infant, born with pulmonary atresia, an intact ventricular septum, and a hypoplastic right ventricle, underwent open pulmonary valvotomy at 2 days of age. A central aortopulmonary shunt was inserted 1 week later. Her postoperative course was complicated by an enterococcal urinary tract infection, which was treated by a 5-day course of intravenous antibiotics.

Two months later, she presented with fever, tachypnea, and oxygen saturation as low as 50% by pulse oximeter. Angiography showed a large thrombus occluding the central shunt and right pulmonary artery. The central shunt was removed and a homograft was inserted between the right ventricle and pulmonary artery. A large clot was evacuated from the right pulmonary artery. Enterococcus was isolated from blood cultures and from the material of the central shunt. The patient was treated with appropriate antibiotics for a total of 6 weeks.

Two weeks after surgical evacuation of the clot, angiography showed that the thrombus had again occluded the right pulmonary artery. Low-dose streptokinase was infused directly into the clot. Fibrinogen levels fell from 3 g/L (pretreatment) to 0.82 g/L during streptokinase treatment, with an increase in levels of fibrinogen degradation products (from <10 to >40 U/L), suggesting that thrombolysis was occurring. Because of a lack of response, the streptokinase treatment was increased to systemic doses, and subsequently urokinase treatment was introduced. After 10 days of therapy, urokinase was discontinued because of bleeding from the site of a Broviac internal jugular catheter. A repeated angiogram showed no resolution of the clot in the right pulmonary artery, which remained completely occluded. Tiny systemic-pulmonary collaterals were noted arising from the right internal mammary arteries. A ventilation-perfusion scan showed adequate ventilation but poor perfusion to the right lung. No further efforts were made to remove the clot, as the infant was maintaining oxygen saturation of about 75%, presumably due to collateral vessel formation, and was gaining weight slowly.

The antithrombin III level (0.63 U/mL) was low in this infant. Protein C activity, which was initially low during the acute illness, became normal during the convalescent phase (Table 3).

Patient 4.—A 2-week-old boy was admitted with apnea, respiratory failure, and shock secondary to respiratory syncytial virus bronchiolitis. After aggressive resuscitation, including intravenous fluids and inotropic support, he was treated with ribavirin and broad-spectrum antibiotics. Three weeks after admission, *Staphylococcus epidermidis* was isolated from blood cultures and was treated with vancomycin hydrochloride. A femoral vein double-lumen catheter was not removed because sterile blood cultures were achieved within 48 hours of vancomycin treatment. While the patient was receiving antibiotics, *Candida albicans* was isolated from urine and blood cultures. An abdominal ultrasound scan showed an echogenic clot (5.1 cm in length) around the catheter in the IVC, extending from the bifurcation of the renal veins to the junction of the hepatic veins. The renal and hepatic veins and the IVC lumen around the clot were patent.

The fungemia was treated with amphotericin B, and low-dose streptokinase was infused into the clot through the venous catheter. Seventy-two hours later, the catheter was removed and systemic urokinase was given intravenously for 96 hours, again without evidence of a reduction in clot size on ultrasound scan. Subsequent examinations showed increased acoustic shadowing suggestive of calcification within the clot. No further attempts at thrombolysis or anticoagulation were made. The infant was subsequently diagnosed as having an immunodeficiency (leukocyte adherence deficiency), but he had no further symptoms related to the thrombosis.

COMMENT

The four cases reported herein represent our total experience with venous and pulmonary artery thrombolysis in the Pediatric Intensive Care Unit at the University of Alberta Hospitals, Edmonton, during the last 2 years. In contrast to our experience with venous and pulmonary artery thrombosis, we have had uniform success in establishing normal peripheral pulses in infants and children with femoral artery occlusions associated with cardiac catheterizations with the use of systemic streptokinase. Children with arterial occlusions after cardiac catheterization have obvious advantages over children with venous thrombosis, in that the cause and time of thrombosis is clearly identifiable, and thrombolytic therapy is usually instituted within 36 hours if the pedal pulses fail to return with heparinization.

Because of the absence of controlled pediatric trials, management of venous thrombosis in childhood is based on extrapolation from the adult experience and isolated pediatric case reports. The literature on the use of thrombolytic agents in children is likely biased by a tendency to report successful therapy rather than failures. The cases reported here emphasize that thrombolytic therapy is not always successful and may cause significant bleeding.

Heparin has been the mainstay of therapy for patients with deep venous thrombosis and may be sufficient for most adult patients with proximal deep venous thrombosis. However, heparin fails to prevent valvular damage in the deep veins and the subsequent manifestations of chronic venous insufficiency. In contrast, rapid clot lysis with thrombolytic agents has been shown to help maintain valvular anatomy and function.[28] This becomes particularly important to consider in the young patient with extensive deep venous thrombosis. Thus, the use of thrombolytic therapy should be considered in these patients in the absence of contraindications.

Thrombolytic therapy consists of the administration of agents (eg, streptokinase, urokinase, and recombinant tissue-type plasminogen activator) that convert the proenzyme plasminogen to the active enzyme plasmin in sufficient concentrations to lyse newly formed thrombi rapidly. The role of thrombolytic therapy in the treatment of adults with thrombotic disease was recently reviewed by Marder and Sherry.[29,30] In aggregated randomized trials, rapid lysis of 75% or more of a thrombus in the proximal veins of the lower extremities has been achieved in 53% of patients given a thrombolytic agent compared with 6% treated with heparin alone.[31] However, the use of thrombolytics cannot be lightly undertaken in view of the potential for serious complications, including an overall risk of bleeding of up to 48% and intracranial hemorrhage in 1% of adults treated.[29]

Vessel recanalization by thrombolysis is unfortunately not uniformly successful in adults, for many reasons. These include the age of the thrombus, the type of vessel involved, the presence or absence of collateral circulation, and whether the vessel is partially or completely occluded. Thrombolysis is, in general, more likely to be successful with fresh clots.[32] However, it is often not possible to date the development of a clot clinically, particularly venous clots, in which symptoms develop slowly. There is little doubt that the thrombi in the cases reported herein were probably long-standing, but they may not differ from those in other reported pediatric cases. The success of thrombolytic therapy may also depend on the type of vessel infused. In decreasing order, success was most likely in grafts, dialysis access, arteries, and veins.[33] Earlier presentation and higher blood flow may contribute to this selective effect. Aortic thrombi, secondary to umbilical arterial catheters, accounted for close to half of the successful reports of thrombolysis (Table 1). This likely reflects the serious clinical presentation of arterial thrombi and frequent use of these catheters. Collateral flow and completely occluded vessels may also reduce local concentrations of the thrombolytic agent and adversely affect the rate of thrombolysis.[34]

Several other related aspects of administration of thrombolytic agents can potentially affect the ultimate outcome: (1) the type of plasminogen activator used, (2) the dose of plasminogen activator, (3) the route of administration, (4) the duration of therapy, (5) plasminogen activity and levels, and (6) whether or not heparin is coadministered with thrombolytics. The three major plasminogen activators currently available for general use include streptokinase, urokinase, and recombinant tissue-type plasminogen activator. Urokinase is probably the agent of choice in children because, unlike streptokinase, it activates plasminogen directly and is nonantigenic. The main theoretical advantage of recombinant tissue-type plasminogen activator over other thrombolytics is its specificity for fibrin and thus potential for decreased bleeding. It is still not clear whether recombinant tissue-type plasminogen activator offers any advantages over conventional thrombolytics in children, and consideration must be also given to cost if a prolonged infusion of recombinant tissue-type plasminogen activator ($1500 per vial) is employed. In addition, the risk of bleeding complications with recombinant tissue-type plasminogen activator in adults appear similar to that of urokinase and streptokinase.[29,30] In children, the relative safety of differing agents is unknown.[22]

Thrombolytic therapy has been administered locally in small doses or systemically in larger doses in children. Pritchard et al[2] described successful clot lysis with the use of low doses of streptokinase (approximately 10% of systemic doses) directly into the occluding lesion. Although standard doses of streptokinase (1000 U/kg per hour) and urokinase (4400 U/kg per hour) were usually employed in children, doses far in excess of these were also used (Table 1). Recently, the use of recombinant tissue-type plasminogen activator was described in children in varying doses from 0.1 to 0.65 mg/kg per hour.[20-22] Since there was no pediatric experience in the literature at the time we used recombinant tissue-type plasminogen activator, we extrapolated from the adult dose and gave an infusion of 0.7 mg/kg per hour, which resulted in a retroperitoneal and intrapleural hemorrhage in our patient Thus, the optimal therapeutic dose regimens for streptokinase, urokinase, and recombinant tissue-type plasminogen activator remain to be determined in newborns, infants, and children.

In adults, most trials of thrombolytic therapy have durations of a few hours up to approximately 24 hours, although durations of several days have been used for extensive deep venous thrombosis.[35] The optimal duration of therapy in pediatric patients is unclear. The range of thrombolytic therapy duration in the pediatric literature for arterial and venous thrombosis varies from a few hours to 12 days (Table 1). We attempted thrombolysis for 10, 3, 10, and 6 days in our four patients.

Corrigan et al[36] showed, by in vitro plasmin generation studies, that newborns needed 11 times the usual concentration of urokinase and five times the usual concentration of recombinant tissue-type plasminogen activator to achieve the minimal activation rate of the adult. The latter likely reflects the low plasminogen concentration in newborns and perhaps dysfunctional fetal plasminogen.[37,38] Although it may be appropriate to correct dysfunctional or low levels of plasminogen by plasma infusions during thrombolysis, this has not always met with success.[24]

There is convincing evidence that therapeutic heparinization is essential in adults after venous thrombolysis, although it is not clear whether concomitant heparinization is helpful. However, bleeding complications are encountered more frequently in those who receive heparin during thrombolytic therapy.[39,40] There is no consistency in the pediatric literature as to whether heparin should be coadministered with thrombolytics (Table 1). We used concomitant heparin empirically when we used low-dose thrombolysis and not during systemic thrombolysis.

Although thrombolytic therapy failed to achieve cannulation in the cases presented here, a trial of such therapy may still be helpful for individual children with significant arterial, pulmonary artery, and deep venous thrombosis, provided there are no absolute contraindications. Early use of thrombolytics is more likely to be associated with successful lysis. Controlled studies are clearly needed to provide the basis for recommendations on optimal use of thrombolytic agents in children. A Canadian national registry of pediatric thrombotic disorders has been begun, and it is estimated that approximately 40 cases per year requiring thrombolysis will be identified. Therapeutic trials will follow, with the goal of optimizing the use of thrombolytic therapy in children.

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Neurodevelopmental Outcome of Term Infants With Intraventricular Hemorrhage

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• **Intraventricular hemorrhage and its sequelae have been reported infrequently in term infants. We investigated the outcome of intraventricular hemorrhage in 15 term infants born between 1982 and 1988. One infant (7%) died. Complications of pregnancy were identified in seven mothers (47%). Age at diagnosis ranged from in utero to 28 days. Clinical presentation included feeding intolerance, fever, jaundice, irritability, and seizures. Severity of hemorrhage was of prognostic value. Of the four children with grade 4 hemorrhage, one died and the three survivors were severely handicapped. Overall, nine (64%) of 14 survivors had no or mild handicap. Perinatal alloimmune thrombocytopenia emerged as the single most important cause of severe hemorrhage and poor outcome. Identification and treatment of these infants must begin in utero if we are to prevent intraventricular hemorrhage and its complications in this group of patients.**

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Intraventricular hemorrhages (IVHs) are a common and significant cause of morbidity and mortality in the preterm infant,[1,2] but a rare event in full-term newborns.[3-7] The increased vascularity and fragility of the subependymal germinal matrix is the cause of most hemorrhages in premature infants.[8] In the full-term infant, multiple sources of hemorrhage have been documented (eg, choroid plexus, tumors, vascular malformations, coagulopathies, and cerebral infarction).[3] Although the long-term sequelae of IVH in premature infants has been studied extensively, the neurodevelopmental outcome of term infants with this condition is still unclear. In previously published studies, the prevalence of survival without handicaps ranged from 16% to 100%.[9,10]

The purpose of this study was to investigate the prevalence, clinical presentation, associated risk factors, and long-term neurodevelopmental outcome of symptomatic IVH in term infants born at or admitted to the Health Sciences Centre, Winnipeg, Manitoba, from January 1982 to December 1988.

PATIENTS AND METHODS

Full-term newborns with an ultrasonographic diagnosis of IVH born at or admitted to the Health Sciences Centre between January 1982 and December 1988 were identified through a computerized search of medical records. The records of the mother and infant were reviewed by one of the authors (L.J.J.) using a standardized data collection form. Gestational age was obtained from the maternal medical record and had been determined with obstetrical ultrasonography or calculated from the date of the last menstrual period. All infants were examined during the first day of life by a pediatrician and were judged to be full term. Infants whose birth weight was above the 97th percentile or below the third percentile for gestation on the Montreal Intrauterine Growth Charts[11] were classified as either large or small for gestational age, respectively. The results of cranial ultrasonography were reviewed and grade of hemorrhage was determined by an independent radiologist using Papile's criteria.[1]

Survivors were examined between ages 2 and 6 years at the Child Development Clinic, Children's Hospital of Winnipeg. Neurodevelopmental status was determined by a developmental pediatrician using the Gesell scales[12] and a standard neurologic examination. An adaptive developmental quotient (DQ) was obtained from the ratio of the child's developmental age to the chronological age multiplied by 100. Neurodevelopmental status was classified as follows: (1) **normal**, adaptive DQ 85 or greater and normal neurologic examination results; (2) **mild** handicap, adaptive DQ 85 or greater with a low score in one developmental subscale (eg, language or motor); (3) **moderate** handicap, adaptive DQ from 71 to 84 alone or adaptive DQ 85 or greater and a significant neurologic and/or sensory deficit compensated for by aids; (4) **severe** handicap, adaptive DQ 70 or less alone or adaptive DQ from 71 to 84 with a significant neurologic and/or sensory deficit not compensated for by aids.

STATISTICAL ANALYSIS

Data were analyzed using Fisher's Exact Test and Spearman's rank correlation coefficient.

RESULTS

We identified 15 infants born at 37 or more weeks' gestation with an ultrasonographic diagnosis of IVH. Of these, eight were born at our center (53%) and seven (47%) had been transferred from other centers. There were 22 420 term live births at the Health Sciences Centre during the same period. The prevalence of symptomatic IVH in full-term infants born at the center was 0.36 per 1000 live births. All of the patients born at our center survived. One (7%) of 15 infants died.

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Table 1.—Perinatal History and Outcome*

Pregnancy Complications	Type of Delivery	Birth Weight, g	Intraventricular Hemorrhage Grade	Outcome			
				Adaptive	Neurologic	Handicap	Other
None	SVD	3350	3	Normal	Normal	None	. . .
None	SVD	3500	3	Normal	Normal	None	. . .
None	SVD	3940	3	Normal	Normal	None	. . .
None	SVD	3000	2	Normal	Normal	Mild	SLD
None	SVD	2860	4	Delay	Hemiparesis	Severe	. . .
None	Forceps	3120	3	Normal	Normal	None	. . .
None	Forceps	3540	2	Normal	Normal	None	. . .
None	Forceps	3990	2	MR	SQ	Severe	. . .
ITP	SVD	3160	3	Normal	Normal	Mild	SLD
PL^{A1}-neg	SVD	2860	4	MR	SQ	Severe	Blind
PL^{A1}-neg†	SVD	2660	4	. . .	. . .	. . .	. . .
PL^{A1}-neg	C section	3530	4	MR	SQ	Severe	Blind
Gestational diabetes	Forceps	4970	2	Normal	Normal	None	. . .
Hydrops	Forceps	2160	3	MR	SQ	Severe	. . .
MVA	C section	3160	2	Normal	Normal	None	. . .

*ITP indicates immune thrombocytopenic purpura; PL^{A1}-neg, platelet antigen 1 negative; MVA, motor vehicle accident; SVD, spontaneous vaginal delivery; C section, cesarean section; adaptive normal, adaptive developmental quotient (DQ) of 85 or greater; adaptive delay, DQ from 71 to 84; MR, mental retardation, DQ of 70 or less; SQ, spastic quadriplegia; and SLD, speech language delay.

†Patient died at age 13 days.

Pregnancy and delivery characteristics are shown in Table 1. Complications of pregnancy were detected in seven mothers (47%). Three women tested negatively for platelet antigen 1, and their infants exhibited alloimmune thrombocytopenia. One mother had idiopathic thrombocytopenic purpura and her infant had a normal platelet count. Presentation was vertex in all cases. The mode of delivery was spontaneous vaginal in eight cases (53%), forceps assisted in five cases (33%), and cesarean section in two cases (14%).

Neonatal characteristics are shown in Table 2. Thirteen infants (87%) were the appropriate size, one (7%) was small for gestational age, and one (7%) was large for gestational age. Of the 15 patients, five (33%) had grade 2 IVH, six (40%) had grade 3, and four (27%) had grade 4. There was no association between severity of IVH and place of birth, fetal presentation, method of delivery, or size for gestational age.

The clinical presentation was generally nonspecific, and at the time of diagnosis patients had one or more of the following problems: seizures in nine patients (60%), fever in seven patients (47%), signs of increased intracranial pressure in four patients (27%), respiratory distress in four patients (27%), hyperbilirubinemia in three patients (20%), feeding difficulties in two patients (13%), dehydration in one patient (7%), and hypoglycemia in one patient (7%). The age at diagnosis ranged from in utero in three patients to 28 days in one patient (median age, 3 days). Twelve infants (80%) were symptomatic by age 3 days, including three infants with alloimmune thrombocytopenia who presented in utero with grade 4 IVH and posthemorrhagic hydrocephalus.

One infant with alloimmune thrombocytopenia died at age 13 days. The 14 survivors were followed up for a mean (±SD) period of 35±16 months (range, 16 to 72 months). Seven patients (50%) had no sequelae, two (14%) had mild handicaps, and five (36%) had severe handicaps. There was a significant association between grade 4 IVH and the occurrence of severe neurologic handicaps ($P<.03$). Of five patients with grade 2 IVH, three (60%) had no sequelae, one (20%) was mildly handicapped, and one (20%) was severely handicapped. Of six patients with grade 3 IVH, four (67%) had no sequelae, one (17%) was mildly handicapped, and one (17%) was severely handicapped. Of four patients with grade 4 IVH, three (75%) survived. All developed hydrocephalus requiring a ventriculoperitoneal shunt and were severely handicapped.

Table 2.—Neonatal Characteristics

Characteristic	Patient Data
Born at Health Sciences Centre, No. (%) of patients	8 (53)
Born at other institutions, No. (%) of patients	7 (47)
Gestational age, wk	
Mean ± SD	39±1.5
Range	37-42
Birth weight, g	
Mean ± SD	3320±659
Range	2160-4970
Male:female ratio	2.75:1
Mean ± SD Apgar scores	
1 min	6±3
5 min	7±2
Intraventricular hemorrhage, No. (%) of patients	
Grade 2	5 (33)
Grade 3	6 (40)
Grade 4	4 (27)
Hydrocephalus, No. (%) of patients	7 (47)

Three additional infants with grade 3 IVH developed hydrocephalus, one of whom required a ventriculoperitoneal shunt. All had normal outcomes.

All infants born to women who tested negatively for platelet antigen 1 developed alloimmune thrombocytopenia and grade 4 IVH and had the worst outcome. One infant died, and the two survivors exhibited severe handicaps with mental retardation, spastic quadriplegia, and blindness. In contrast, the child born to a woman with idiopathic thrombocytopenic purpura developed grade 3 IVH despite having a normal platelet count, and at follow-up had a significant language delay but was otherwise healthy (Table 1).

COMMENT

Although IVH has been reported primarily as a problem of the preterm infant, we now know that it is also an important, albeit less frequent, entity in full-term infants. The neurodevelopmental outcome of term infants with this condition is still unclear.

We investigated the prevalence, clinical presentation, associated risk factors, and long-term neurodevelopmental outcome of symptomatic IVH in term infants born at or admitted to a tertiary care center during a 7-year period. A prevalence of 0.36 per 1000 live births may underestimate the actual occurrence of IVH in this population. Although a computerized search of medical records has the potential for data loss, we cross-checked the information obtained in this manner with that obtained from a review of the High Risk Newborn Follow-Up Program database, making any omissions less likely. Since only infants suspected of having intracranial disease underwent ultrasonography, asymptomatic cases would not have been detected. However, earlier reports[4,13] have shown that the more severe forms of IVH are invariably symptomatic, reducing the possibility that we missed a patient with significant but clinically undetectable IVH. For these reasons, we believe that the prevalence of IVH in our referral center likely reflects the prevalence of IVH in term infants in the general population.

A normal pregnancy and delivery history should not exclude the diagnosis of IVH. Five mothers (33%) in this study had uncomplicated pregnancies and deliveries. Two of their infants became symptomatic after initial hospital discharge. Nonaccidental trauma was considered and investigated, but never proved. No other cause of IVH was ever found.

There was a significant association between grade 4 IVH and the occurrence of severe neurologic handicaps. The presence of hydrocephalus or need for a ventriculoperitoneal shunt did not worsen the outcome of children with grade 3 IVH. Since we did not have any patients with grade 4 IVH without hydrocephalus, we do not know how their outcome might have been affected by this complication.

Although the incidence of perinatal alloimmune thrombocytopenia is low, 0.2 to 1 per 1000 births,[14] it poses major difficulties for clinicians. Platelet-specific antibodies can cross the placenta as early as 14 weeks' gestation,[15] causing hemorrhagic complications in utero. The treatment of fetuses with perinatal alloimmune thrombocytopenia is controversial. Several approaches have been suggested to prevent neurologic damage in offspring of women who have had a previously affected infant. Nicolini et al[16] advocated prophylactic weekly transfusions of antigen-negative small-volume platelet concentrates to severely thrombocytopenic fetus from 26 weeks' gestation until elective cesarean section is performed at 32 weeks' gestation or later.

Daffos et al[17] disputed this approach for the following reasons: severe thrombocytopenia may be present by 20 weeks' gestation, therapy is complicated due to the short life span of platelets, weekly maternal platelet pheresis is debilitating, and there is a significant risk of viral infection and autoimmunization from the use of donor platelets. Brussel et al[18] found that following diagnosis via percutaneous fetal blood sampling, antenatal weekly treatment of the mother with intravenous immunoglobulin was effective in elevating fetal platelet count and preventing intracranial hemorrhages. This could be done as early as 20 weeks' gestation if required.

Fetal scalp sampling for platelet counts to determine the mode of delivery is inaccurate and cesarean section will only prevent IVH in some infants with perinatal alloimmune thrombocytopenia.[19] Following delivery, different modalities of treatment have been used to treat the affected newborn. These have included corticosteroids, exchange transfusion, transfusion of random compatible or maternal platelets, and high-dose IV gamma globulin.[14] Transfusion of compatible antigen-negative platelets alone or combined with the administration of intravenous immune globulins have been reported to be of benefit and appear to be the treatment of choice.[20,21]

Intraventricular hemorrhage is an important clinical entity in the full-term infant. It can occur in an otherwise normal pregnancy and delivery and, therefore, a high index of suspicion needs to be maintained. Our findings suggest a low mortality (7%) and generally favorable outcome with nine (64%) of 14 survivors having no or mild handicap. We found a significant association between grade 4 IVH and poor neurodevelopmental outcome. Perinatal alloimmune thrombocytopenia emerged as the single most important cause of severe hemorrhage and poor outcome. Identification and treatment of these infants must begin in utero if we are to prevent IVH and its complications in this group of patients.

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BOOK REVIEW

Fits and Faints (Clinics in Developmental Medicine, No. 109)

By John B. P. Stephenson, 212 pp, $55, New York, NY, Cambridge University Press, 1990.

The British have a way with words, as indicated in this book's title. The book is written by a pediatric neurologist at the Royal Hospital for Sick Children in Glasgow, Scotland. In response to widespread overdiagnosis of epilepsy and lack of understanding of various "spells" in children, the author has compiled a highly useful monograph. It is refreshing in this day and age of high-tech neurodiagnostic evaluations to see this fine clinical approach to important and common clinical problems.

Chapters include reviews of epileptic and nonepileptic seizures, differential diagnosis, syncopes, anoxic seizures, psychogenic seizures, fits and faints in special settings, and prognosis. The special settings include sleep, gastroesophageal reflux, bathing and water immersion, blood and gore, head injury, startle-surprise-or-fright, schools, places of worship, and hairdressers. Each chapter is enlivened by case histories to illustrate the author's clinical points.

Noting that "some neurologists have a remarkable zeal for the early treatment of epileptic seizures," the author provides reasonable and sage advice on the office delineation of the variety of nonseizure states. Clinicians who see children with "spells" will benefit from the author's wisdom and this excellent compilation of sage, clinical judgment.

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Outcome of Nonoperative Management of Splenic Injury With Nuclear Scanning

Clinical Significance of Persistent Abnormalities

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• Uncertainties remain about the frequency and need for diagnostic imaging following recovery from splenic injury with nonoperative management. To gain further understanding, the final appearance of the splenic roentgenographic image was evaluated in 20 consecutive children (mean age, 10.1 years) undergoing serial studies up to 70 weeks following injury. A total of 65 technetium 99m sulfur colloid scans, including 45 follow-up studies, were obtained and evaluated. By 20 weeks following injury, six patients (30%) were normal, four (20%) demonstrated minimal residual effects, and 10 (50%) had significantly improved, leaving some persistent abnormality. None of the patients in the last group showed any clinical problem. No distinctions could be made by comparing the severity of the initial injury with a persisting imaging defect. We conclude that clinical considerations alone should determine whether any follow-up imaging be performed in children recovering from splenic injury.

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The nonoperative management of splenic injury in the pediatric patient in clinically stable condition has become uniformly accepted as a safe method for preserving splenic function. Although the management of the immediate postinjury phase has been standardized,[1] questions of long-term follow-up, including the incidence and risk of residual splenic defects, which may predispose to reinjury, have been raised and are often influential in recommending a conservative approach to resuming full activities. To gain further relevant data on this issue, a prospective study of splenic injury after hospitalization was carried out to determine the actual pattern of splenic healing and the significance of persisting abnormalities seen on nuclear scan in 20 consecutive patients.

MATERIALS AND METHODS

Twenty children (13 boys and seven girls) between ages 2 and 18 years (mean age, 10.1 years) with blunt splenic injury were treated without surgery at the Yale–New Haven (Conn) Hospital between January 1985 and September 1988. All patients had stable vital signs on admission, or their conditions improved following initial resuscitation. The diagnosis of splenic injury was initially made with either computed tomography (CT) or technetium 99m sulfur-colloid scanning. The patients received the usual protocol for nonoperative treatment of bed rest, intravenous fluids, and monitoring.[1]

A technetium 99m sulfur-colloid scan was obtained within 7 days of presentation in patients who previously underwent CT, and a second technetium 99m scan was obtained in all patients within the first 2 weeks following injury. Follow-up studies were performed at varying intervals over a maximum of 6 months following the injury, or until the results of the follow-up scan appeared normal. Ultrasonography was not used in follow-up during this study.

The initial scans were classified according to the distribution of abnormal uptake (focal or diffuse), shape of defect (linear or wedge), and size of the defect (grade 1, 2, or 3) by an unbiased observer (N.S.R.) who was not aware of the eventual outcome. Grade 1 injuries were focal and limited to less than 25% of the estimated splenic volume; grade 2 injuries were medium-sized, involving up to 50% of the spleen; and grade 3 injuries were more extensive. By assessing the appearance of the follow-up scans, an attempt was made to determine whether the defects resolved at a uniform rate and whether resolution correlated with clinical recovery. The overall usefulness of the nuclear scan and long-term follow-up of splenic injuries managed without surgery were evaluated. The clinical status of the patients was also determined at the time of follow-up scanning.

RESULTS

The diagnosis of splenic injury was made with either CT (six patients) or technetium 99m sulfur-colloid scanning (14 patients). Additional injuries recognized included left-sided rib fractures and left-sided pneumothorax in four patients and bilateral pubic rami fractures in one patient. One clavicle fracture, one subarachnoid hemorrhage, two femoral shaft fractures, and one tibia-fibula fracture were also observed in five patients. There were no significant associated intra-abdominal injuries.

A total of 65 nuclear scans, including 45 follow-up studies, were obtained and evaluated. The duration of follow-up ranged from 1 week to 70 weeks, with between two and six scans obtained per patient. The distribution, shape, and size of the initial defects are listed below and show the injury to be typically visualized as a small, wedge-shaped defect involving a focal portion of the spleen.

The findings on repeated scans were organized into four periods following injury to determine the number of scan results that had become normal, showed improvement, or remained unchanged (Fig 1). Several scans obtained within the first 12 weeks tended to show improvement or become normal, while additional follow-up studies performed after 12 weeks of the injury in four (57%) of seven patients showed a persisting but small defect. The earliest normal scan result was obtained 7 weeks after injury in a patient with an initial focal, wedge, grade 1 defect. By 20 weeks, the results of six scans were completely normal. Four of these injuries were initially grade 1, while the other two were grade 3. Minimal persistent defects tended to be more common in those patients with more serious inju-

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ries. By 20 weeks, four scans demonstrated minimal residual defects. Two of these injuries were initially grade 2 and two were grade 3. The results of the remaining scans had all significantly improved. Persistent abnormalities were observed as late as 46 and 70 weeks after the injury in only two (22%) of nine patients with grade 1 defects.

The conditions of all patients had clinically improved within 1 week following injury. The mean duration of hospital stay was 14.4 days and 7.8 days for patients with isolated splenic injury. There were no cases of abdominal splenosis, splenic cyst formation, or delayed rupture as determined by nuclear imaging. All patients returned to full activities within 12 weeks following their injury, and have remained well during a minimum follow-up period of 2 years. No clinical distinctions could be made by comparing the severity of the initial injury with the presence of a persisting defect on the nuclear scan. Figures 2 through 4 show serial scans in three representative patients.

COMMENT

The trend toward nonoperative management of splenic injury[1,2] has increased with the recognized risk of overwhelming postsplenectomy sepsis in the pediatric age group[3-5] and accumulated experience that bleeding from the injured spleen will cease in the patient in hemodynamically stable condition.[1,2] The issue of long-term follow-up has been discussed in the literature,[6-9] but the incidence of a persisting splenic defect, the risk of reinjury, and guidelines to establish the frequency of imaging follow-up remain undetermined. Initially, pediatric surgeons advocated the use of technetium 99m sulfur-colloid scanning to make the diagnosis of splenic injury and to warn of potential complications in patients receiving nonoperative treatment.[10]

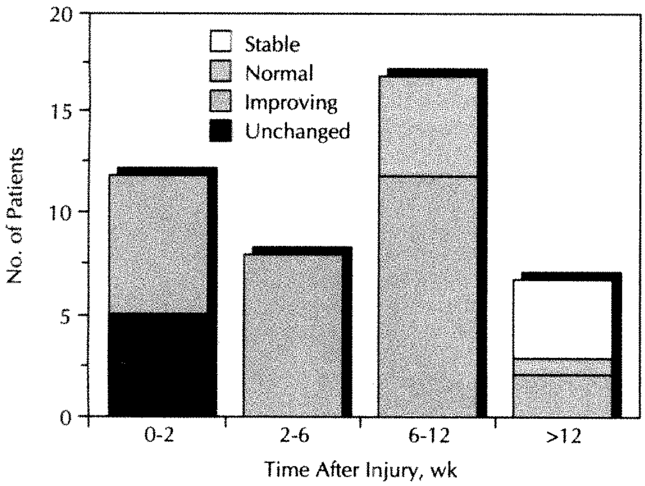

Fig 1.—*Technetium 99m sulfur-colloid scan results following splenic injury.*

In 1978, Howman-Giles et al[11] reported that "long-term follow-up using scintiscans is useful to assess resolution and development of complications." Splenic scans were obtained in 22 of their 28 patients, 14 of whom had minimal residual defects, but there were no late complications. Implications of their findings were not discussed. Since there have been reports of "delayed splenic" rupture in the older literature,[12-15] Sziklas et al[16] suggested follow-up studies for predictive monitoring so that patients with enlarging defects who may experience rupture might be prospectively identified.[17] Despite these warnings, serial nuclear imaging showing the evolution of a pseudocyst from a subcapsular hematoma has not been reported, to our knowledge.

Using nuclear scanning instead of CT in our follow-up studies may be regarded as controversial since CT is uniformly believed to be a better diagnostic test, and it also shows other solid organ injuries and occasionally bowel injuries. For the purposes of this study, we chose nuclear scanning since it provided excellent definition of an evolving splenic injury, was more easily available, and involved a reduced dosage of radiation exposure compared with CT.

Our data suggest that splenic imaging abnormalities resolve at varying rates, with a tendency for smaller defects to resolve more rapidly than larger lesions. Within 2 to 3 weeks after injury, all scan findings had improved. With further follow-up, some of the scan findings normalized while others continued to improve or show a persistent stable defect. Persistent stable defects were identified in some patients months after they returned to regular activities, suggesting that small abnormalities on multiple follow-up scans have little, if any, clinical significance. None of our patients developed later complications, such

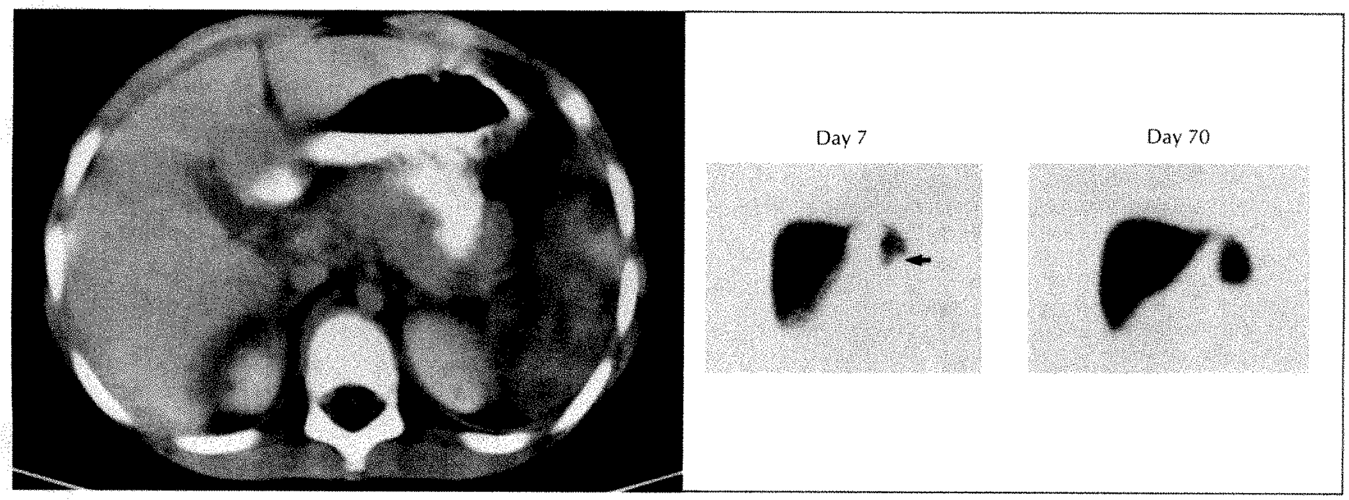

Fig 2.—*Scans of a 5-year-old boy with a large splenic laceration after a motor vehicle accident. Left, Abdominal computed tomographic scan on day 1 shows diffuse grade 3 injury. Right, Scan on day 7 shows a grade 3 defect in the inferior pole of the spleen that had resolved by day 70. The patient was discharged on day 9 and did well.*

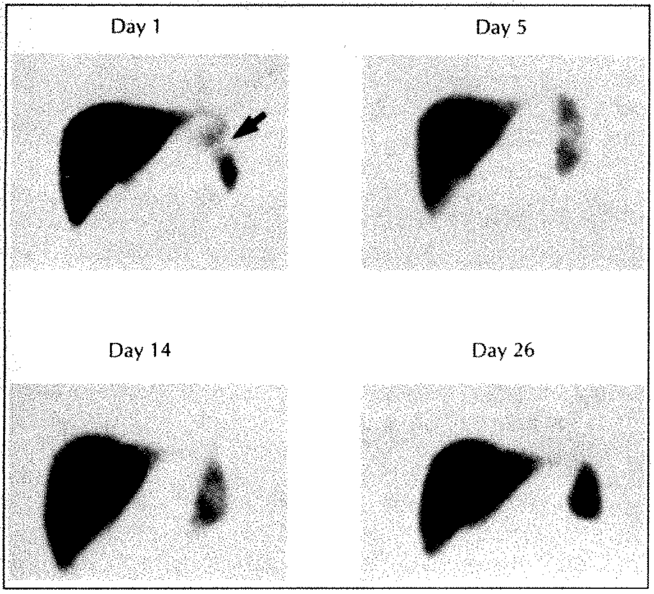

Fig 3.—*Technetium scans of a 10-year-old boy with an initial isolated, focal, wedge, grade 3 defect. Successive scans on days 5 and 14 show partial resolution of the abnormality. By day 26, the defect had disappeared.*

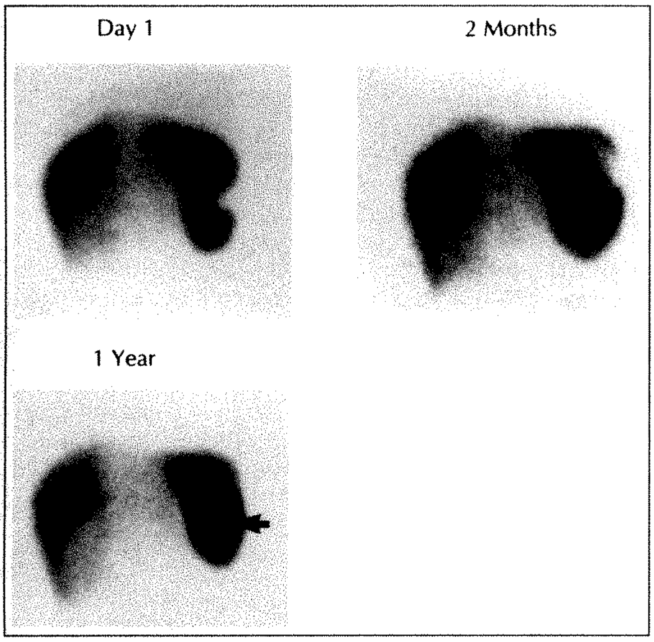

Fig 4.—*Technetium scans of a 7-year-old boy. Scan on day 1 shows a fracture displacement of the inferior aspect of the spleen on initial scan. Follow-up 2 months after the injury shows partial resolution. Follow-up 1 year after the injury demonstrates a minimal residual defect (arrow). Ultrasonography showed no evidence of a developing pseudocyst.*

as delayed rupture of the spleen or pseudocyst, during a 2- to 5-year follow-up.

IMPLICATIONS

Technetium 99m sulfur-colloid scanning proved to be a reliable imaging study in defining persisting defects following splenic injury and is equivalent to CT when a single follow-up of the splenic injury is the primary indication for performing the study. We continue to prefer CT as the initial diagnostic test for evaluating splenic injury, and based on the results of this study are not recommending that a second study routinely be performed. Increasing experience with ultrasonography in splenic injury may eventually make this modality interchangeable with nuclear imaging or CT for the follow-up evaluation, but our experience with ultrasonography is limited.

Our data suggest that clinical considerations alone should determine whether follow-up imaging in patients recovering from splenic injury be performed. Certainly, only one follow-up study is required to determine if the splenic defect is stable or beginning to resolve. When uncertainty exists, the study should be performed between 2 and 6 weeks following injury.

Subsequent imaging is indicated only when enlargement or other significant change of the original defect is demonstrated in the first follow-up study, or in patients with persisting pain, tenderness, or splenomegaly. Some persistent splenic defects may be anatomic variants having no long-term significance and not increasing the risk of reinjury.

Our current practice, based on this clinical experience and imaging data, is to restrict patients from participating in school gymnastics and contact sports for 3 months following injury. Children may resume normal play and other routine activities as their clinical condition improves.

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Internal Carotid Artery Blood Flow Velocities Before, During, and After Extracorporeal Membrane Oxygenation

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• Blood flow velocities in the internal carotid arteries were studied with pulsed Doppler in 25 neonatal patients (birth weight range, 2600 to 4100 g) who had extracorporeal membrane oxygenation (ECMO). Time averaged mean systolic, mean diastolic, and mean blood flow velocities were calculated. Five infants had right common carotid artery reconstruction. Blood flow velocities measured in 15 healthy full-term infants were used as controls. Findings during ECMO included the following: (1) forward flow in the right internal carotid artery in 50% of the infants; (2) significant increase in the mean diastolic and the mean flow velocities (48% and 128%, respectively) in the left internal carotid artery when compared with pre-ECMO and control infants' values; (3) the elevation in the mean and the mean diastolic velocities was associated with changes in the $PaCO_2$ and with an increase in the diastolic blood pressure; and (4) forward blood velocities in the right internal carotid artery were comparable with blood velocities in the left internal carotid artery and with the blood velocities of control infants. After ECMO, the mean diastolic velocity in the left internal carotid artery decreased significantly, but it remained elevated when compared with pre-ECMO values. Infants with right common carotid reconstruction had blood velocities in the right internal carotid artery comparable with the simultaneous blood velocities in the left internal carotid artery and to the blood velocities of control infants. Twenty-eight percent of the infants had major neuroanatomic lesions. Right or left preponderance was not noted. No association between blood velocity values in the internal carotid arteries or flow direction and the presence or the absence of brain lesions was noted.

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Extracorporeal membrane oxygenation (ECMO) is commonly used in the management of neonatal pulmonary failure.[1,2] Although infants requiring this therapy may have preexistent neurologic injury, the high incidence of acquired neuroanatomic abnormalities in these infants raises the concern that ECMO may adversely affect the cerebral circulation increasing the risk for brain lesions and impaired neurodevelopment.[3-20]

Venoarterial bypass, the neonatal ECMO procedure used most commonly, requires cannulation and ligation of the right common carotid artery and the right internal jugular vein. Following ligation of the right common carotid artery, blood flow direction in the right internal carotid artery can be either forward or retrograde depending on whether blood flow arises from collateral flow from the left external carotid circulation or from the circle of Willis.

Several Doppler studies of the cerebral circulation in neonatal patients who have undergone ECMO have reported on the direction of blood flow in the cerebral arteries and/or the pulsatility index.[21-30] To our knowledge, quantification of flow velocities in the internal carotid arteries before, during, and after ECMO, and their comparison with those of healthy newborn infants, have not been described. Reconstruction of the right common carotid artery has been performed to restore pre-ECMO cerebral hemodynamics.[14,15,30,31] To our knowledge, only one study measuring the blood velocities in the internal carotid arteries shortly after right common carotid reconstruction has been published.[31]

This study was performed to do the following: (1) compare the blood velocities in the internal carotid arteries of infants requiring ECMO with the blood velocities of healthy newborn infants; (2) quantify changes in the blood flow velocities of the internal carotid arteries before, during, and after ECMO; (3) assess the direction of the blood flow in the right internal carotid artery during and after ECMO; and (4) evaluate in infants with right common carotid reconstruction the blood velocities in the right and left internal carotid arteries and compare the results with those of healthy newborn infants.

METHODS

Population

The cerebral blood flow velocities in the internal carotid arteries of 25 neonatal patients who had undergone ECMO (mean birth weight, 3300 g; range, 2600 to 4100 g; mean gestational age, 40 weeks; range, 36 to 42 weeks) were reviewed. All infants met established ECMO selection criteria.[1,2]

Arterial blood gas values, blood pressures, ventilator settings, and ECMO pump rate were recorded during the blood flow ve-

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Table 1.—Blood Flow Velocities in the Internal Carotid Arteries: ECMO*

			During			After		
	Control LICA	Before LICA	LICA	RICA F Flow	RICA R Flow	LICA	RICA F Flow	RICA R Flow
n	15	7	24	12	12	15	9†	6
SFV, cm/s	35.9 ± 1.8	33.7 ± 4.3	39.7 ± 2.3	32.3 ± 5.0	−14.0 ± 1.7	41.0 ± 2.4	32.1 ± 3.6	−17.5 ± 2.9
MFV, cm/s	24.9 ± 1.6	22.7 ± 3.1	31.6 ± 2.1	26.1 ± 4.1	−11.5 ± 1.2	29.5 ± 2.1	23.0 ± 2.9	−12.1 ± 2.1
DFV, cm/s	17.1 ± 1.3	11.9 ± 1.9	26.5 ± 2.1	22.2 ± 3.7	−9.8 ± 1.0	19.4 ± 1.9	15.4 ± 2.5	−7.9 ± 1.4

*Values are mean ± SE. ECMO indicates extracorporeal membrane oxygenation; LICA, left internal carotid artery; RICA F Flow, right internal carotid artery forward flow; RICA R Flow, right internal carotid artery reverse flow; SFV, systolic flow velocity; MFV, mean flow velocity; and DFV, diastolic flow velocity.

†Includes five infants with repair of the right common carotid artery. Blood velocities in these five patients were similar to the velocities of the four patients without right common carotid artery repair.

Table 2.—Left Internal Carotid Artery Paired Comparisons of Blood Flow Velocities, Blood Gases, and Blood Pressures: ECMO*

	Before	During	*P*	During	After	*P*
n	6	6		14	14	
SFV, cm/s	23.0 ± 4.7	40.6 ± 4.6	NS	41.2 ± 3.1	39.3 ± 1.9	NS
MFV, cm/s	21.7 ± 3.6	32.3 ± 4.8	.045	32.2 ± 2.7	28.1 ± 1.6	NS
DFV, cm/s	11.6 ± 2.2	26.5 ± 5.1	.02	27.1 ± 3.0	18.3 ± 1.7	<.02
pH	7.63 ± 0.03	7.64 ± 0.02	NS	7.57 ± 0.02	7.44 ± 0.02	<.001
$PaCO_2$, mm Hg	27 ± 3.7	30 ± 3.0	NS	36 ± 2.4	53 ± 1.7	<.001
BE, mEq/L	9.5 ± 2.0	11.4 ± 1.8	NS	11.1 ± 1.5	10.0 ± 1.4	NS
PaO_2, mm Hg	37 ± 7.1	390 ± 21.2	<.001	395 ± 11.5	77 ± 6.8	<.001
SBP, mm Hg	61 ± 4.2	74 ± 6.2	NS	68 ± 3.8	64 ± 2.1	NS
MBP, mm Hg	51 ± 3.7	55 ± 4.6	NS	57 ± 3.4	51 ± 1.8	NS
DBP, mm Hg	43 ± 3.2	49 ± 3.4	.03	50 ± 3.2	41 ± 1.8	.017

*Values are mean ± SE. ECMO indicates extracorporeal membrane oxygenation; SFV, mean systolic flow velocity; NS, not significant; MFV, mean flow velocity; DFV, mean diastolic flow velocity; BE, base excess; SBP, systolic blood pressure; MBP, mean blood pressure; and DBP, diastolic blood pressure.

locity studies. Fourteen of the 25 infants had meconium aspiration syndrome, six had respiratory distress syndrome, four had pneumonia, and one had a congenital diaphragmatic hernia. Fifteen healthy full-term infants (mean birth weight, 3400 g; range, 2700 to 3900 g) born after normal pregnancy, labor, and delivery and with unremarkable neonatal courses were studied at random after obtaining parental consent.

Cerebral Blood Flow Velocity Measurements

The right and left internal carotid arteries were insonated from the anterior fontanelle with a duplex sector scanner equipped with a triple-frequency transducer (5, 7.5, and 10 MHz) and range-gated pulsed Doppler (Ultramark 8 [ATL], Bothell, Wash). The smallest sample volume available in this (Ultramark 8) (1.5 mm) was used.

The sample volume was positioned in a sector of the internal carotid artery immediately below the diaphragma sellae (where the main axis of the artery is perpendicular to the axial plane). To maintain the same angle of incidence in all of the studies, the direction of the ultrasound beam was kept perpendicular to the axial plane of the head and the ultrasound image was rotated until the area of the artery to be sampled was insonated.

Using this procedure, the angle of insonation is always close to zero since the transducer is directly apposed to the flow in the carotid artery. Measurements of the blood velocities using this technique are independent of the angle of incidence and they are highly reproducible (coefficient of variation, 3.5%; coefficient of repeatability among observers, 0.98).[32] Color Doppler was used in selected cases to confirm the direction of flow in the right internal carotid artery during and after ECMO. The mean systolic, the mean diastolic, and the mean blood flow velocities were calculated as a function of time using a computerized system.

The cerebral blood velocities were studied as clinical condition allowed. Because of the critical status of the patients, few had studies before ECMO. Most of these patients had studies in the left internal carotid artery alone since in newborn infants, right and left internal carotid arteries have similar blood velocities.[33-35] Several patients were not studied after ECMO since they were transferred back to their referring hospitals shortly after decannulation.

Imaging Studies

Central nervous system real-time ultrasound images through the fontanelles were obtained at least once before ECMO, daily while receiving ECMO, and at least once after ECMO. The brain anatomy was visualized in the coronal, sagittal, and axial planes with a modification of the technique described previously.[36] Cranial computed tomographic examinations done by clinical indication in 10 survivors were reviewed (median age at study, 13 days; range, 8 to 45 days; and median time after ECMO, 7 days; range, 2 to 40 days).

The presence or absence of the following neuroanatomic lesions diagnosed by echoencephalography, computed tomography, or both was noted in each infant: nonhemorrhagic ischemic lesions in the white matter and/or the cortex, cerebellar hemorrhages and/or infarctions, classic intraventricular-periventricular hemorrhages, intraparenchymal hemorrhages and/or hemorrhagic infarctions, subarachnoid hemorrhages, ventricular dilatation, hydrocephalus, and widening of the subarachnoid spaces.

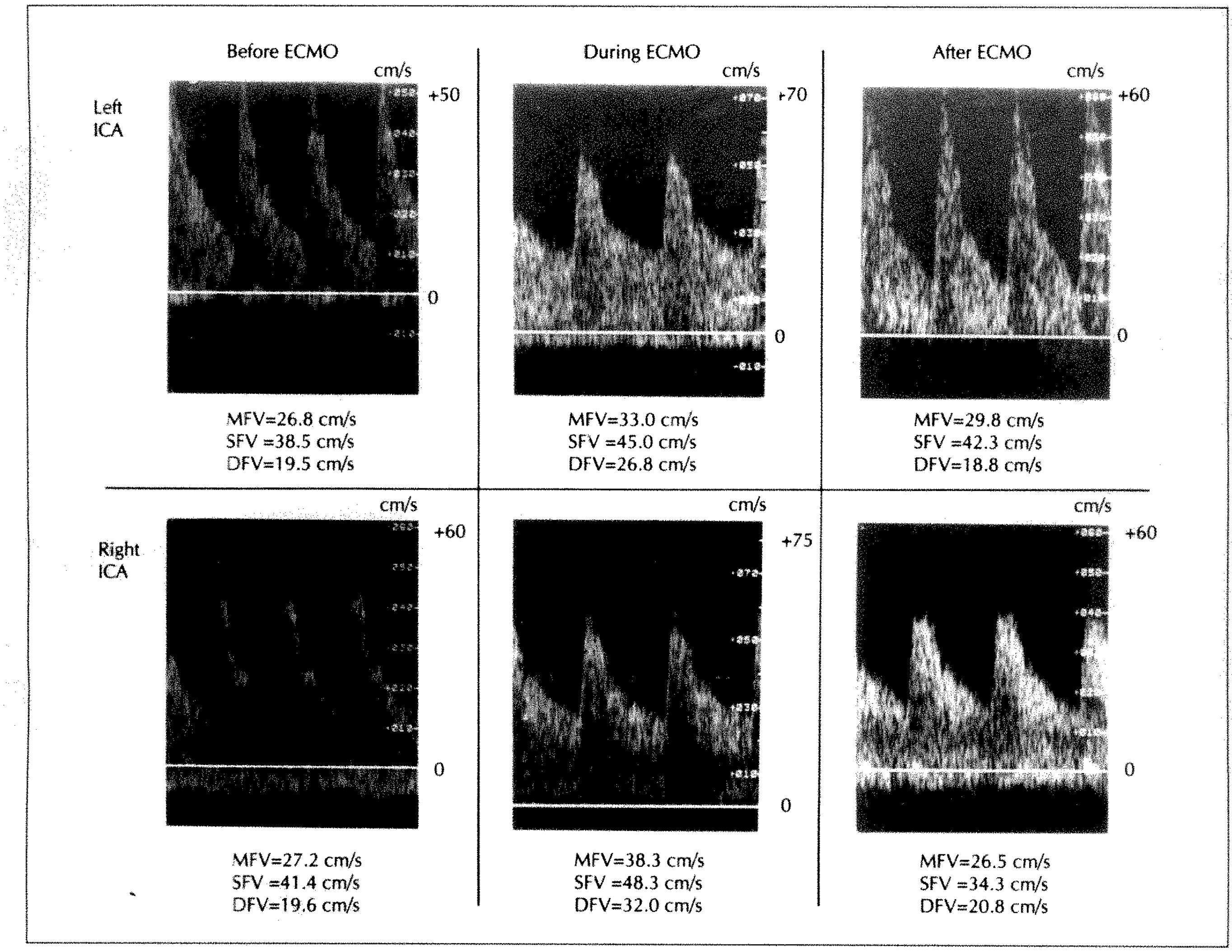

Fig 1.—*Blood flow velocities in the left and right internal carotid arteries measured in one patient before, during, and after extracorporeal membrane oxygenation (ECMO). During ECMO, the mean flow velocity (MFV) increased 23%, the mean diastolic flow velocity (DFV) increased 37%, and the mean systolic flow velocity (SFV) increased 17% in the left internal carotid. The blood flow in the right internal carotid artery remained forward. In this artery, the mean velocity increased 41% and the mean diastolic velocity increased 61%. Left and right internal carotid arteries had similar blood flow velocities. After ECMO, the mean diastolic velocity decreased in both arteries, but the mean velocity was similar to pre-ECMO values.*

Statistical Analysis

Unpaired *t* tests were used to compare the blood velocities of controls vs infants requiring ECMO and the blood velocities in the right internal carotid artery with the blood velocities in the left internal carotid artery. Paired *t* tests were used to compare the blood velocities, blood gas values, and blood pressures before, during, and after ECMO. Linear regression was used to study the association between changes in the blood velocities and the blood gas values, pump rate, and arterial blood pressures. Values are reported as the mean±SEM.

RESULTS

Seven of the 25 infants had studies before, 24 infants had studies during, and 15 infants had studies after ECMO (Table 1). Five infants underwent right common carotid reconstruction following decannulation. Two infants died during ECMO for a mortality of 8.3%. The blood velocities were measured at 2.3±0.6 hours before ECMO, at 26.7±5.4 hours after starting ECMO, and at 23.5±8.1 hours after ECMO. Mean ECMO pump rate at the time of blood velocity measurements was 104±5.6 mL/kg per minute. Mean duration of bypass was 102±9.9 hours.

Before ECMO, infants were hypocarbic (Table 2) and had lower mean diastolic blood velocities than control infants ($P<.04$; Table 1). During ECMO, the mean and the mean diastolic blood velocities in the left internal carotid artery were significantly higher than control (27%, $P=.03$ for the mean and 55%, $P=.003$ for the mean diastolic, respectively; Table 1).

In six patients with measurements before and during ECMO, the mean and the mean diastolic blood velocities in the left internal carotid were significantly higher than their pre-ECMO values ($P=.05$ and $P=.02$, respectively; Table 2). The mean increase for the mean velocity was 49% and for the mean diastolic velocity was 128% (Fig 1).

During ECMO, these six patients had a significant rise in the PaO_2 ($P<.001$) and in the diastolic blood pressure ($P=.03$) (Table 2). In these patients, the mean airway pressure was reduced from 25±5 mm Hg before ECMO to 9.8±2 mm Hg during ECMO ($P=.04$). No significant changes were seen in the absolute values of the $PaCO_2$ or the pH. However, a significant positive association was noted between the percentage of change of the mean blood

Table 3.—Blood Flow Velocities in the Right and Left Internal Carotid Arteries During and After ECMO*

	ECMO							
	During				After			
	RICA Reverse Flow		RICA Forward Flow		RICA Reverse Flow		RICA Forward Flow	
	LICA	RICA	LICA	RICA	LICA	RICA	LICA	RICA
n	12	12	12	12	6	6	9	9†
SFV, cm/s	37.5±2.3	−14.0±1.7	41.8±4.1	32.3±5.0	44.2±4.7	−17.5±2.9	38.9±2.5	32.1±3.6
MFV, cm/s	29.2±2.0	−11.5±1.2	33.9±3.5	26.1±4.1	31.9±4.2	−12.1±2.1	27.8±2.1	23.0±2.9
DFV, cm/s	23.8±2.0	−9.8±1.0	29.3±3.7	22.2±3.7	21.3±4.1	−7.9±1.4	18.1±1.8	15.4±2.5

*Values are mean±SE. ECMO indicates extracorporeal membrane oxygenation; SFV, mean systolic flow velocity; MFV, mean flow velocity; DFV, mean diastolic flow velocity; LICA, left internal carotid artery; and RICA, right internal carotid artery. For each group, the values in the LICA and RICA correspond to the same patients.

†Includes five infants with repair of the right common carotid artery.

Table 4.—Blood Flow Velocities in Infants With Common Carotid Artery Repair (N=5)*

	LICA	RICA
SFV, cm/s	34.0±0.7	37.0±1.5
MFV, cm/s	23.0±0.3	26.0±0.8
DFV, cm/s	15.0±1.1	17.0±1.2

*Values are mean±SE. SFV, mean systolic flow velocity; MFV, mean flow velocity; DFV, mean diastolic flow velocity; LICA, left internal carotid artery; and RICA, right internal carotid artery.

velocity and the percentage of change in the Pa_{CO_2} ($r = .77$, $P = .02$). During ECMO, the blood velocities in the left internal carotid artery did not correlate with the pump rate.

Fifty percent (12/24) of the infants had forward flow in the right carotid artery during ECMO (Table 1). The blood velocities in the infants with forward or retrograde flow in the right internal carotid artery were obtained at similar intervals after cannulation (interval for forward flow, 23.3±8.1 hours; interval for reverse flow, 30.7±7.2 hours). Infants with forward or reverse flow in the right internal carotid artery had similar pump rates, blood gas values, and blood pressures when blood velocities were studied. The birth weight, gestational age, and incidence of the main pathologic conditions were also comparable in both groups.

The forward blood velocities in the right internal carotid artery were like the blood velocities found in the internal carotid artery of healthy infants (Table 1). The forward blood velocities in the right internal carotid artery during ECMO were also similar to the concurrent blood velocities in the left internal carotid (Fig 1, Table 3). However, a trend toward lower forward blood velocities in the right internal carotid artery (Table 3) was noted.

Retrograde mean blood velocity in the right internal carotid artery was 38% of the simultaneous forward mean blood velocity in the left internal carotid artery and 46% of the mean velocity of healthy newborn infants (Fig 2, Tables 1 and 3). The blood velocities in the left internal carotid artery during ECMO were similar in infants with forward or reverse flow in the right internal carotid artery (Table 3).

After ECMO a significant decrease of the Pa_{O_2} ($P < .001$), the pH ($P < .001$), and the diastolic blood pressure ($P = .017$), and a significant increase of the Pa_{CO_2} ($P < .001$) was noted (Table 2). Only the mean diastolic blood velocity in the left internal carotid artery decreased significantly ($P < .02$) (Figs 1 and 2, Table 2). However, this velocity was still higher than pre-ECMO ($P = .025$) and was similar to the mean diastolic velocity of control infants (Table 1).

After ECMO, the forward blood velocities in the right internal carotid artery were comparable with the simultaneous blood velocities in the left internal carotid artery and to the blood velocities of healthy newborn infants (Tables 1 and 3). Infants with forward or reverse flow in the right internal carotid artery after ECMO had similar blood velocities in the left internal carotid artery (Table 3). The blood velocities in the right internal carotid artery of

Table 5.—Brain Lesions*

	Pre-ECMO	ECMO			
	n	R	L	B	N
Nonhemorrhagic ischemic lesions	0	2	1	3	6
Cerebellar hemorrhage infarction	0	...	...	1	1
Classic intraperiventricular hemorrhage	2	2	4	5	11
Subarachnoid hemorrhage	2	...	...	...	6
Ventricular dilatation	2	...	...	10	10
Hydrocephalus	0	...	...	2	2
Widening of the subarachnoid spaces	0	...	...	...	17

*R indicates right; L, left; B, bilateral; and ECMO, extracorporeal membrane oxygenation.

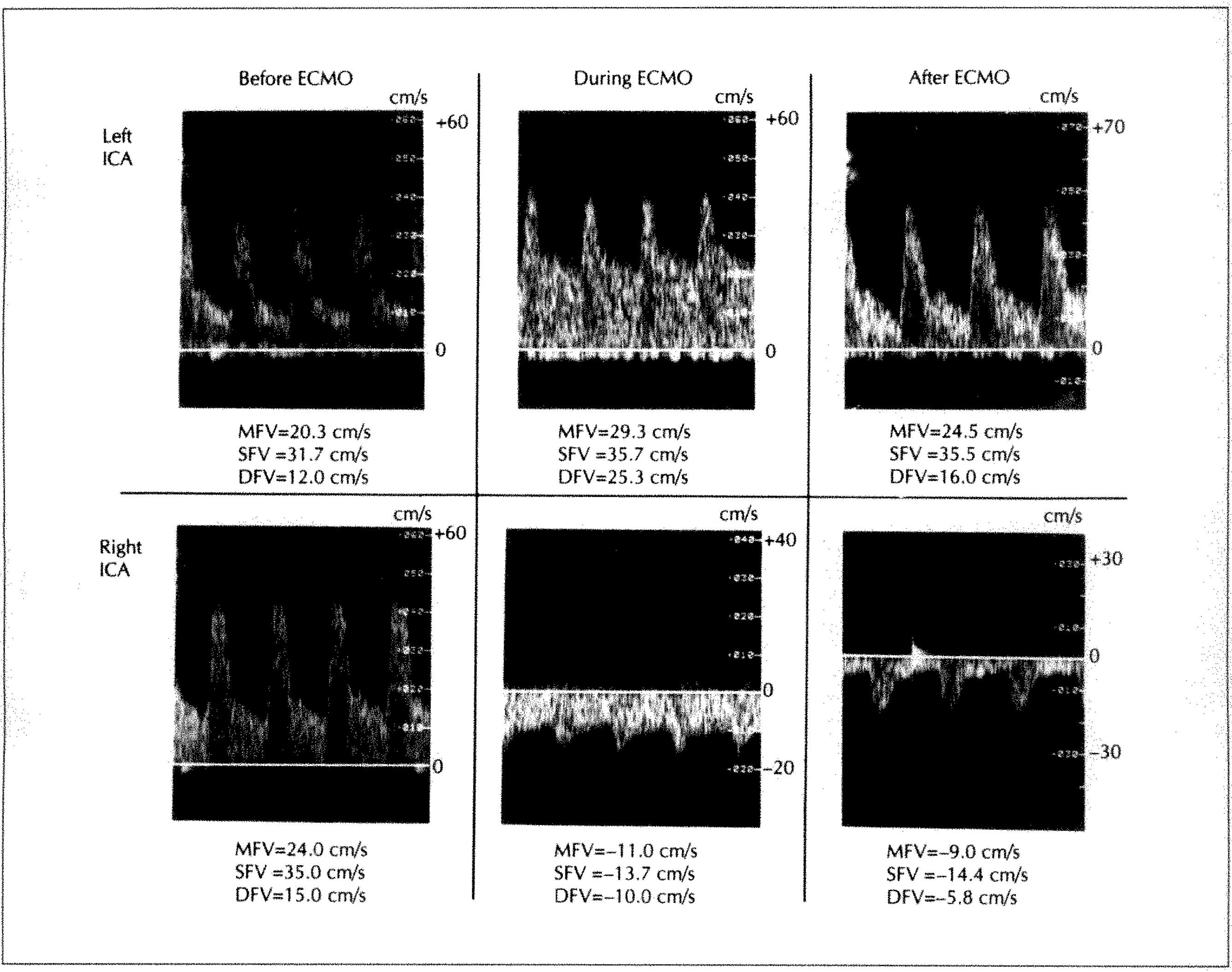

Fig 2.—*Blood flow velocities in the left and right internal carotid arteries measured in one patient before, during, and after extracorporeal membrane oxygenation (ECMO). During ECMO, mean flow velocity (MFV) and mean diastolic flow velocity (DFV) in the left internal carotid artery increased 44% and 111%, respectively; meanwhile, the mean systolic flow velocity (SFV) increased only 13%. Reverse flow in the right internal carotid developed. Retrograde right mean velocity was 38% of simultaneous forward left mean velocity. After ECMO, right internal carotid artery flow was still reversed. Left internal carotid artery mean diastolic velocity decreased 37%. However, mean velocity remained elevated when compared with pre-ECMO values. Reverse mean velocity in the right internal carotid artery was 37% of the mean velocity in the left internal carotid artery.*

infants with right common carotid reconstruction (measured at 6.7±2.5 hours after repair) were similar to the concomitant blood velocities in the left internal carotid artery and to the blood velocities of control infants (Tables 1 and 4).

Eighteen infants had one or more neuroanatomic abnormalities diagnosed during or after ECMO (Table 5). Seven infants (28%) had major lesions: six had white matter and/or cortical infarctions, and one had cerebellar infarction or hemorrhage. Two of the previous infants had development of hydrocephalus. All the intraventricular-periventricular hemorrhages were small and the dilatation of the ventricles was mild (between 8 and 14 mm in the axial plane at the atria). There was no preponderance of right-sided lesions. Eight of the 18 patients had one or more brain lesions before ECMO (Table 5).

Neuroanatomic abnormalities were not associated with the blood velocities in the internal carotid arteries. Infants with reverse flow in the right internal carotid artery during ECMO had the same incidence (three of 12) of ischemic and/or hemorrhagic parenchymal lesions as the infants with forward flow in the right internal carotid artery (four of 12). The infants with major lesions had similar blood velocities in the left internal carotid artery as infants without cerebral injury. No new neuroanatomic abnormalities were detected after common carotid reconstruction (interval between reconstruction and last study, 19.8±10.6 days).

COMMENT

Previous studies have suggested that the anterior and posterior communicating arteries (circle of Willis) are the primary sources of blood flow to the right hemisphere during ECMO.[23-27] This study shows that the left external carotid artery is an important collateral to the right internal carotid circulation, since 50% of the infants had forward flow in the right internal carotid artery during ECMO. Furthermore, the forward blood velocities during and after ECMO in the right internal carotid artery were similar to the simultaneous blood velocities in the left internal carotid artery and to the blood velocities of healthy infants. These results are similar to those of Taylor et al[26] who reported a 37% incidence of forward flow in the right internal carotid artery during ECMO. In contrast, Mitchell et al[27] found forward flow in the right internal carotid artery in only 9% of infants receiving ECMO.

There is no clear explanation why infants may have development of forward or reverse flow in the right internal carotid artery after ligation of the common carotid artery. Birth weight, gestational age, and primary pathologic conditions were similar in both groups. Furthermore, the infants had similar blood gas values, blood pressures, and pump flow rates at the time the blood velocities were studied during ECMO.

Since retrograde blood flow in the right internal carotid artery could produce a "steal" of blood from the circle of Willis, it could be assumed that infants with forward flow in the right internal carotid artery may be less prone to brain ischemia. In our study, retrograde mean blood velocity was 38% of the simultaneous forward mean velocity in the left internal carotid artery and 46% of the mean blood velocity of healthy infants. However, infants with reverse flow in the right internal carotid artery during ECMO had a similar incidence of ischemic and/or hemorrhagic brain lesions as infants with forward flow in the right internal carotid artery. Furthermore, the incidence of major lesions in the right and left hemispheres was similar, which agrees with previous studies reporting brain lesions in infants treated with ECMO.[3-7,9-14] Our data suggest that right-sided brain injury may occur after common carotid artery ligation since four infants had development of ischemic or hemorrhagic lesions in the right hemisphere during ECMO. This agrees with the study of Schumacher et al.[8] Of 59 ECMO survivors, they found eight infants with evidence of right hemispheric brain injury after ligation of the common carotid artery. Changes in the blood velocity and blood flow direction in the right internal carotid artery seem to have little predictive significance regarding the development of brain lesions in neonatal patients who have undergone ECMO. The problem of determining precisely the presence of brain lesions before bypass can be difficult.[8] Because of the systemic heparinization during ECMO, ischemic or small hemorrhagic brain lesions undetected by echoencephalography before ECMO can become hemorrhagic facilitating their diagnosis with ultrasonography.

Before ECMO, the infants were hypocarbic, which may account for a lower mean diastolic velocity than in control infants. During ECMO, an increase in the mean velocity was caused by an elevation of the mean diastolic velocity. These findings agree with reports showing a significant decrease in the pulsatility index in the anterior and middle cerebral arteries during ECMO.[22,26,28,29]

In our study, the percentage increase in the mean velocity occurring after the onset of ECMO was associated with an increase in the diastolic blood pressure and correlated with changes in $PaCO_2$. After ECMO, mean diastolic velocity in the left internal carotid artery decreased but the mean velocity remained elevated when compared with healthy infants. These changes were associated with a decrease of the diastolic blood pressure and a significant increase in the $PaCO_2$. Cerebral vascular resistance fluctuations caused by the changes in the $PaCO_2$ along with the variations of the diastolic blood pressure (likely caused by the nonpulsatile pump) may explain the significant changes of the mean and mean diastolic velocities in the left internal carotid arteries during and after ECMO.

Right common carotid artery reconstruction following ECMO has been found effective in restoring patency of the artery.[13,14,30,31] Two recent reports describe antegrade blood flow in the right internal carotid artery following common carotid reconstruction.[30,31] This study confirms these results and indicates that shortly after reanastomosis, the blood velocities in the right internal carotid artery are similar to the concomitant blood velocities in the left internal carotid artery and to the blood velocities of healthy newborn infants. However, since our measurements were made only a few days after reconstruction, we cannot speculate on the long-term outcome of this procedure in terms of the development of stenosis or occlusion at the site of repair and the development of new brain lesions.

CONCLUSION

In summary, before ECMO, infants requiring bypass had lower mean diastolic velocity in the left internal carotid artery than controls. During ECMO, mean diastolic and mean flow velocities in the left internal carotid artery increased by 49% and 128%, respectively. This rise was associated with changes in the $PaCO_2$ and with an increase of the diastolic blood pressure. Fifty percent of infants had forward flow in the right internal carotid artery during ECMO with velocities comparable to the simultaneous velocities in the left internal carotid artery and with control infants' blood velocities indicating the presence of large collaterals between the right and left external carotid artery circulations. Shortly after right common carotid artery repair, right internal carotid artery flow was forward in all infants with blood velocities comparable with the simultaneous blood velocities in the left internal carotid artery and with those of control infants. Twenty-eight percent of the infants had major neuroanatomic lesions. Right or left preponderance was not noted. No association was noted between internal carotid artery blood velocities or right internal carotid flow direction and the presence or absence of brain lesions. Apparently, cerebral blood flow velocity changes in the internal carotid arteries have little predictive value regarding the development of brain lesions in patients who have undergone ECMO.

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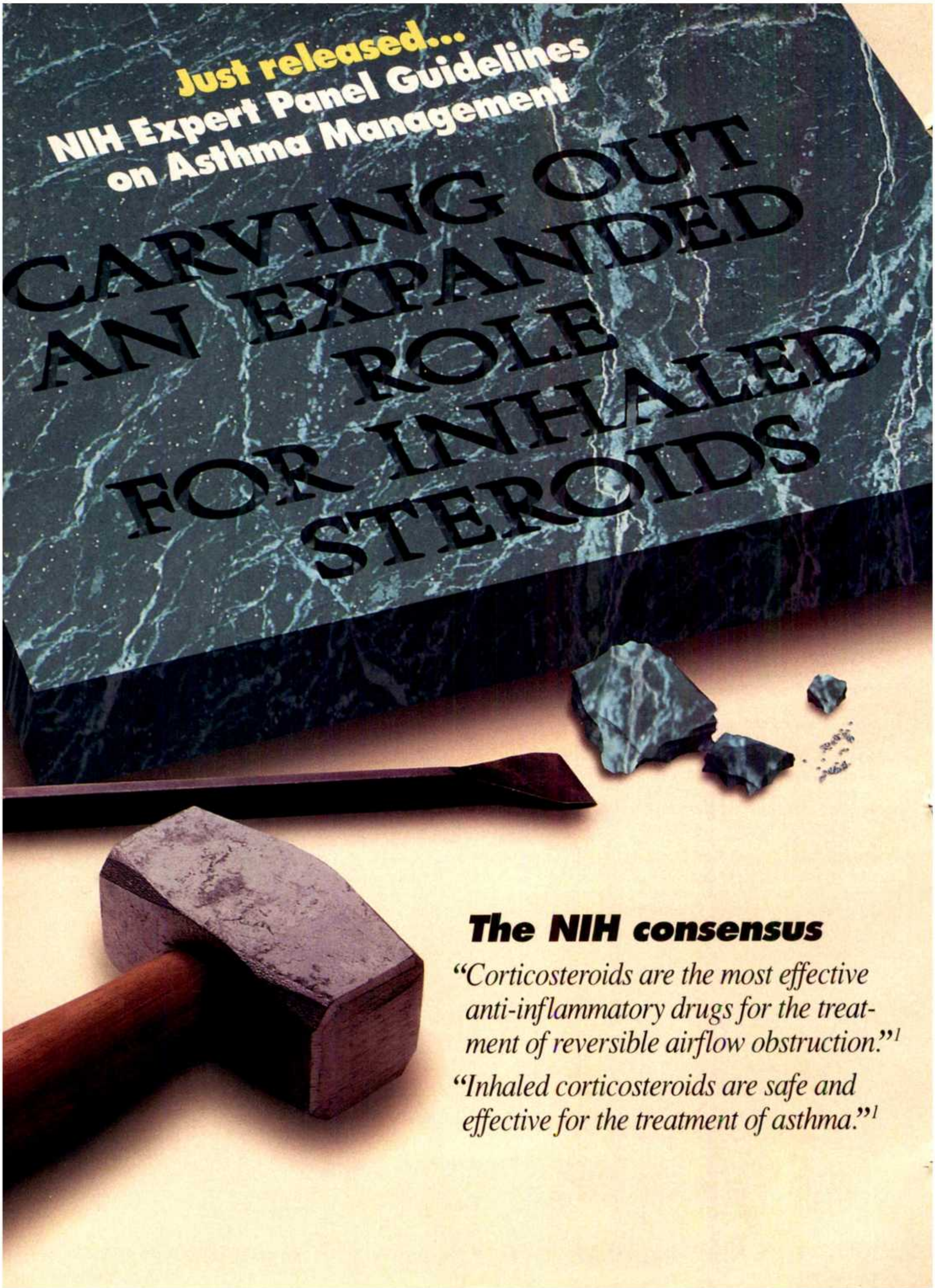

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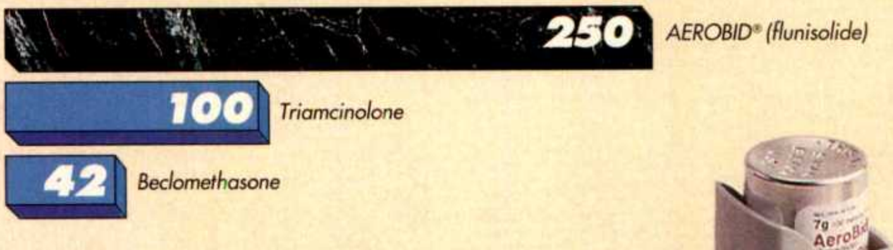

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Effective asthma control BID

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CONTRAINDICATIONS

AeroBid Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with Candida albicans or Aspergillus niger have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral Candida may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler.

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function.

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice. An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors.

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General:* flu (10%); *Mouth and Throat:* sore throat (20%); *Nervous System:* headache (25%); *Respiratory:* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); *Special Senses:* unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations; *Gastrointestinal:* abdominal pain, heartburn; *General:* chest pain, decreased appetite, edema, fever; *Mouth and Throat:* Candida infection; *Nervous System:* dizziness, irritability, nervousness, shakiness; *Reproductive:* menstrual disturbances; *Respiratory:* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*; *Skin:* eczema, itching (pruritus), rash; *Special Senses:* ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; *Cardiovascular:* hypertension, tachycardia; *Gastrointestinal:* constipation, dyspepsia, gas; *Hemic/Lymph:* capillary fragility, enlarged lymph nodes; *Mouth and Throat:* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; *Nervous System:* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo; *Respiratory:* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort; *Skin:* acne, hives, or urticaria; *Special Senses:* blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath.

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*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

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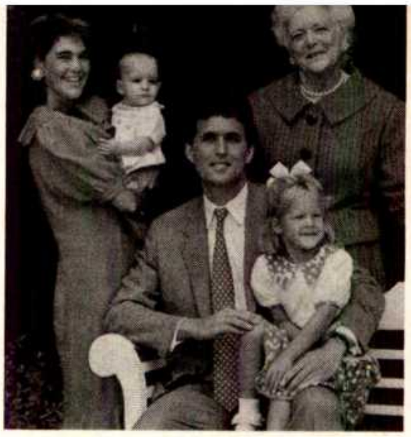

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Coaches

A Missing Link in the Health Care System

Bruce R. Brown, Jr, MD, Stephen A. Butterfield, PhD

• The number of children and adolescents who participate in interscholastic athletics demands attention to the quality of the coaching they receive and to the opportunities that the athlete-coach relationship provides for modification of high-risk behaviors, social skills training, and character formation. Although the need for coaches has increased due to the advent of girls' athletic programs, which was mandated by Title IX legislation, only a minority of states require certification for coaches who work in school systems. Four coaching curricula are summarized and contrasted: the American Coaching Effectiveness Program, the curriculum of the National Youth Sports Coaches Association, the Athletic Health Care System, and the Coach Effectiveness Training Program. Recommendations for coach certification by states, physician advocacy for coaching standards, and improved sports medicine services are discussed.

(*AJDC*. 1992;146:211-217)

Although it is reasonable to object to our society's glorification of sport compared with academics or other nonathletic activities, the sheer number of children and adolescents participating in organized sport mandates paying attention to the quality of their experience. Because of sports' increased availability compared with other areas of endeavor, athletic participation provides an opportunity for cooperative, interactive learning and adult mentoring, which may offer the greatest benefit to the greatest number at the lowest cost. However, that economy ought not to result in the widespread neglect of coaches and the diminution of the potential that they represent to our children.

During the last decade, the morbidity rates of premature and unprotected sexual intercourse, violence, suicide, substance abuse, and low self-esteem have emerged as determinants for the health of school-aged children, particularly adolescents. The urgent need to intervene has resulted in the recruitment of schools as an efficient site for identification and treatment. Health education curricula have been expanded to encompass issues that were formerly off-limits, the direct-care activities of the school nurse have been increased, substance abuse services are regularly available in schools, and school-based clinics now provide primary health care for teenagers—services that often include treatment of sexually transmitted diseases, contraceptive needs, and mental health disorders. Although school nurses, substance abuse counselors, and health educators have been recruited to help provide services for children and adolescents who attend school, coaches have been largely ignored as a health care resource. This article argues for the recruitment of coaches as members of an extended health care team for children and adolescents and reviews curricula that provide training to justify that role. We hope the data presented herein will allow physicians to better advocate for trained coaches in both schools and communities.

THE BENEFITS OF SPORTS PARTICIPATION

The value of sports participation with respect to character development has been endorsed by such diverse commentators as Greek philosophers and television sports announcers. Given the almost universal experience of some form of organized sports participation, it is not unexpected that personal opinion about the value of sports for an individual abounds in the lay press (*Bangor Daily News*. November 14, 1990:11) and in pediatric textbooks.[1] Echoing their classical predecessors, advocates list as potential benefits the opportunities to gain self-confidence,[1] to have "maturing experiences,"[2] to foster transracial or transethnic friendships (*Bangor Daily News*. November 14, 1990:11), and to develop models for later parenting or employer-employee relationships. Clearly, sports participation encourages fitness in a population

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Purpose.—*This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.*

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whose overall fitness is suspect.[3] Sports provide the opportunity for supervised cooperative and competitive social contact that prepares participants for more varied social interactions as adults and that may, in some athletes, decrease high-risk behaviors (*Bangor Daily News*. November 14, 1990:11). For the few gifted high school athletes who will compete professionally (estimated to be one in 10 000), organized athletics begins training for a career.

Participation in school-sponsored athletics is not without risk, however. Beyond the risk of physical injury, sports may be a significant source of stress for those who choose to compete. Nonetheless, attempts to quantitate stress in athletics and compare it with other life events appear to refute the reputation of athletic competition as the preeminent stressor for school-age athletes. Sports participation, even in individual events, was found to be less stressful than performing a musical solo,[4] and in a 1984 study of 2400 fifth graders, "not being good enough at sports" ranked only 17th as a life event that made preadolescents feel bad.[5] According to patients surveyed in a general adolescent clinic, Green et al[6] found that athletic participation was not in the top 20 of negative life events. However, for the late-maturing athlete inappropriately competing against skeletally mature peers or for the child who endures the scathing criticism of an untrained coach, the stress of participation may be considerable and is often undetected.

Paradoxically, sports also may benefit those who do not compete. High school sports figure prominently in the mythology of the hometown and can promote community cohesiveness and self-image.[7] Similar effects are possible in microenvironments of neighborhoods, school systems, or civic organizations that identify with the teams they sponsor. Overidentification with or glorification of sports certainly may detract, though, from the recognition of other competencies in individuals or institutions and can divert financial resources away from activities that serve other cohorts of children and adolescents.

EPIDEMIOLOGY OF INJURIES

In the 1988-1989 academic year, the National Federation of State High School Associations[8] reported that 5 256 196 boys and girls participated in interscholastic athletics. In some communities, this number comprised up to half of the boys and one third of the girls of high school age.[2] In 1981, more than 17 million children participated in community-based athletic programs[9] such as Little League baseball or peewee hockey, and that number is currently estimated to have risen to 20 million.[10]

Calvert[11] estimated that during the 1975-1976 academic year, nearly 600 000 injuries were experienced by the 5 million boys and girls in the United States who participated in high school sports. Fifteen percent (90 000) of these injuries resulted in the athlete's missing several games for 3 weeks. Powell[12] maintains that by 1987, more than 600 000 injuries occurred in football alone. Zaricznyj et al[13] analyzed the injury rate to school-aged children in a single midwestern community from school first aid reports, insurance claims, and medical records. They found that while children and adolescents were injured more frequently during participation in unorganized sports, injuries due to school sports participation resulted in 15% of 1576 injuries observed. Community sports participation constituted 7% (n = 116) of the remaining injuries to athletes. For those who participated in school-based sports, the injury rate was 120 injuries per 1000 students. In Europe, reports by the parent or athlete reveals that organized sports are responsible for more injuries than physical education classes or unsupervised sports activities, constituting 62% of the incidence.[1]

Multiple studies have examined the epidemiologic characteristics of athletic injury. Backx et al[14] have found a greater frequency of injury during practice, while others found competition to produce more injuries.[13,15] However, these differences may be a function of the medical astuteness of the observer,[16] failure to control for hours of participation or sport,[15] definition of injury, or injury recall by coaches.

Athletes who participate in collision sports experience, not surprisingly, the greatest frequency of injury. Football, a sport offered by 78% of US high schools, is responsible for 28 to 81 injuries (defined as requiring removal from practice or competition) per 100 participants per season[13,17] and, in one referral clinic, was responsible for 12 times the number of injuries seen in other sports.[18] Wrestling causes nearly the same rate of injuries as football, approximately 75 injuries per 100 participants.[17] (Injuries sustained while playing ice hockey were not surveyed in the above studies.) Gymnastics is responsible for the greatest frequency of injuries to girls, approximately 40 injuries per 100 participants. Basketball, track and field, and soccer occupy the middle range of 30 to 40 injuries per 100 participants, with swimming and tennis causing fewer than 10 injuries per 100 participants on the high school level.[17]

DEMOGRAPHICS OF COACHING

Notwithstanding the potential importance of interscholastic sports to the school and community, there is a growing concern among administrators, scholars, parents, and the public regarding the qualifications of coaches. The growth in number and type of interscholastic sport has been exponential in the post–World War II era and this growth has accelerated with the enactment of Title IX legislation that guaranteed equal access and opportunity for female athletes. These factors combined to create a demand for coaches that could not be met from the ranks of most public school faculties. As a result, school officials have been compelled to look to the community at large to fill coaching vacancies. In the process, a substantial cadre of untrained adults have entered the public school athletic system (*Newsweek*. October 29, 1990:12).[19]

Although no national data currently exist detailing the extent to which community coaches are employed by schools, unpublished master's thesis data are available for specific states. In middle-sized high schools in Wisconsin, the number of community coaches nearly tripled from 1978 to 1982.[20] Schwan[21] investigated the professional preparation of high school basketball coaches in Oregon in the 1983-1984 academic year and found that 10% of boys' coaches and more than 29% of girls' coaches were not faculty members in their respective schools. He reported similar findings for Minnesota and North Dakota.[21] Abbott and Butterfield[19] observed that among all high school basketball coaches in Maine, the percentage of community coaches ranged from 17.1% (boys' varsity) to 51.2% (boys' freshman). They also found that although most of these coaches were college graduates, few had training in first aid or cardiopulmonary resuscitation.

Another area of concern relative to coaching demographics has been the declining number of women coaches. Ironically, this has occurred in an era of unprecedented sports opportunity for female athletes. Again, in the absence of national data, evidence from individual states provides the only available frame of reference. In Iowa, where girls' basketball often draws larger crowds than boys' games, Mathes[22] reported at the 1982 American Association for Health, Physical Eduction, Recreation, and Dance convention that only 12% of all girls' basketball teams were coached by women. When all girls' sports were counted, the percentage dropped to 6%. Similar findings were reported for Florida.[23] Disconcertingly, the paucity of women coaches is likely to continue or worsen if female athletes perceive few opportunities for advancement.

The degree to which coaches are underappreciated with respect to their potential role in preventive health care for young athletes is suggested by an analysis of the amount of time that students spend with coaches. A study[24] of practice time for four of the most popular high school sports in the United States revealed that athletes spent an average of 9.88 hours per week in practice (range, 4.5 to 14.5 hours). The average player-coach ratio for these sessions was approximately one coach per seven players. The competitive season for these sports ranged from 12 to 52 weeks (mean, 33 weeks). Simple arithmetic indicates that the average athlete spent 326 hours of practice time under the coach's supervision during a typical season. If this number is compared with the 156 hours spent in a high school English class over the course of an academic year, the potential influence of the coach is obvious. In fact, it is likely that athletes spend more time with coaches in an activity that has health consequences than they spend with school nurses, health educators, guidance counselors, and physicians combined. Some parents may even argue that their children spend more time interacting with coaches than they do with them. Despite this investment of time, communities, school systems, and Departments of Education on the state and federal level have generally failed to sanctify the coach-athlete relationship by requiring minimum levels of competency in coaching or sports medicine.[25]

Coaches are revered by American culture if not by most athletes. On the college level (and probably on other levels as well), having played for certain coaches is as strong a recommendation as having done a residency or fellowship under a particular chairperson or director. Coaches have a credibility and an attentive audience that few other adults who deal with children and teenagers regularly enjoy.[26] In fact, it is a developmental certainty that elementary schoolchildren will often vest nonrelated adults, usually teachers or coaches, with a greater veracity than that which is accorded their parents. Given the lengthening list of high-risk behaviors[27,28] for which children, especially adolescents, are currently at risk, it is especially important to recruit and train coaches to take advantage of those "pregnant moments" so they can provide guidance on subjects such as tobacco, anabolic steroid, alcohol and other drug use, responsible sexuality, avoidance of violence, and the importance of education. Through relationships with their coaches, athletes can practice child-adult interactions in a milieu free of academic and parental symbolism. Coaching may even be the best preadult opportunity to prepare for employer-employee relationships.

Table 1.—Coaching Certification by State, 1986-1987*

States Requiring Coaching Certification for Some or All Coaches	States Requiring Neither Teaching Certificate Nor Coaching Certificate for Coaches
Arkansas	Hawaii
Iowa	Indiana
Minnesota	Maine
New York	Massachusetts
Wyoming	Michigan
	New Hampshire
	North Dakota
	Ohio
	Oregon
	Pennsylvania
	Rhode Island
	Vermont

*Adapted from Sisly and Wiese.[25]

COACHING CERTIFICATION

In light of the potential benefit that coaches offer to the health of the athletes under their supervision, it seems especially important to examine the training and minimum levels of competence that coaches are required to attain before being allowed to work in the community or school setting.

Coaching certification involves the attainment of minimal levels of testable knowledge and skill in first aid, cardiopulmonary resuscitation, sports psychology, pedagogy, and acute care for athletic injuries. Developing standards for coaches has been recommended for the variable or absent training that many public school and community coaches have brought to the playing field. In Maine for instance, 75% of the state's athletic directors favored certification.[19] However, in many other states, athletic directors preferred eliminating or minimizing training standards for coaches.[29] In New York, all teachers *other* than physical educators who coach must hold a coaching license. In Minnesota, only varsity head coaches are required to hold a coaching license and a teaching certificate, while Iowa mandated that all head coaches of major sports (ie, football, basketball, baseball, and track and field) hold both a coaching endorsement and a teaching certificate. By 1987, 25 states required all school coaches to hold a teaching certificate, but only Wyoming required all coaches to hold coaching certification. Moreover, only eight states that had established standards for coaches considered adopting coaching certification as one of those standards. In all, 12 states required neither a teaching certificate nor a coaching certificate for some or all of their school coaches (Table 1).[25] This is unfortunate because coaching certification obviously provides a measure of quality control for school-aged athletes similar to that which is required of teachers.

COACHING CURRICULA

Despite the large numbers of children and adolescents participating in sports and the increasing development of coaching pedagogy as an academic discipline, little systematic data have been collected that examine "average" coaching behaviors, athlete's observations of and preferences for certain coaching methods, or the effectiveness of the few model curricula currently designed to increase the coaches' knowledge, change coaching behavior, or lower injury rates.

Currently, four coaching education curricula are available in the United States that have achieved recognition through promotion by their developers, government sponsorship, or by articles in the sports medicine and physical education literature. Of these, two offer education for coaches in multiple aspects of coaching, while one focuses on sports medicine exclusively. The last, and most thoroughly documented from an effectiveness viewpoint, offers training exclusively in sports psychology.

American Coaching Effectiveness Program

The curriculum that has received the widest name recognition is the American Coaching Effectiveness Program (ACEP). Developed in 1981 by sports psychologist Rainer Martens, PhD, and marketed by him through Human Kinetics Publishing, Champaign, Ill, ACEP initially addressed the needs of the untrained high school and community coach by providing a basic text and brief seminar on sound principles of teaching sports to children and adolescents. Because of its economy in time and expense, ACEP has appealed to public school systems and communities that are committed to improving the quality of coaching in their recreational programs. With the advent of the Leader Level curriculum (see below), the National Federation of Inter-Scholastic Coaches Association is currently promoting ACEP training by offering instruction at its national meetings. Coaches who complete the program are eligible for increased liability coverage through the association's insurance plan.

The ACEP format has been expanded into three levels. The Volunteer curriculum targets youth league coaches and involves a 6-hour seminar, a textbook, and an open-book examination. The Leader Level program, designed for the high school or experienced coach, uses a similar format involving an 8-hour seminar, text, and take-home examination. Additional Leader Level curricula available include sports first aid, sport techniques and tactics, and sports science. Certification is provided to those who complete the Volunteer and Leader Level training and pass the take-home examination but, obviously, does not ensure competency or the translation of coaching theory into effective coaching behavior. The ACEP Master Level program involves nine separate content areas: sport psychology, sport law, teaching sports skills, time management, sport psychology, sport administration, sport injury, sport rehabilitation, and nutrition and weight control.

There has been sparse documentation of the effectiveness of ACEP in the coaching pedagogy literature. Burton et al[30] presented their evaluation of the impact of ACEP Volunteer Level training on a cohort of 22 youth basketball coaches and compared them with a similar group of untrained coaches. The mean age for both groups was 21.4 years. The authors found that while ACEP coaches did not show the anticipated differences in coaching methods, they encouraged significantly greater socialization skills, were less win-oriented, and rated themselves more understanding of players' emotions than non-ACEP coaches. These differences in sport psychology were also reflected in the athletes' perceptions. They identified the ACEP coach as being more adept at communicating with them, their parents, and officials than the untrained coach. There were, however, no significant differences in enjoyment measures between athletes of untrained and ACEP coaches and, surprisingly, there were no observed differences between the two groups of coaches in the employment of praise or criticism. All coaches in the study used 20 times more criticism and four times more punishment than praise!

National Youth Sports Coaches Association Curriculum

The National Youth Sports Coaches Association (NYSCA) developed a sports education curriculum for coaches aimed primarily at preteen school community sports programs. Developed as a nonprofit association in 1981, the NYSCA assists state and local member associations in organizing community sports and in training and supporting its coaches and parents. In 1987, the NYSCA, along with a consortium of parents, coaches, federal drug enforcement officials, and the National Parent-Teachers Association, developed the "National Standards for Youth Sports," which now constitutes the foundation for their curriculum.

There are 11 "national standards." They emphasize proper sports pedagogy, appropriate developmental expectations for young athletes, coach certification, education about alcohol and other drugs, and appropriate modeling of substance use by parents and coaches. These standards also emphasize how to educate and train parents to be supportive of the child athlete.

More than 2000 communities in 43 states have developed local chapters of NYSCA and offered its primary and follow-up training. Initially, the coach participates in a 3-hour session on generic issues of youth sport coaching, followed by a 3-hour session on a specific sport. The format of the training in each case involves video presentations followed by a discussion with a trained facilitator. The 3-hour session on generic principles of youth coaching includes sports psychology, the coach as a role model for young athletes and their parents, the coach's role as a modifier of high-risk behaviors in young athletes, the role of winning in youth sports, and basic concepts in sports medicine.

Upon successful completion of a test at the end of the training, the coach is allowed to sign the "Coach's Code of Ethics" (Table 2). By paying a $15 per year membership fee, the coach automatically receives a $500 000 liability insurance policy and other modest benefits. To maintain certification, the coach must attend a second- and a third-year training program modeled after the first but dealing with advanced concepts in coaching pedagogy, psychology, and sports medicine. Video and print resources for parents are also provided by the NYSCA and coaches are trained in how to educate parents and recruit them to join in a partnership for quality youth sports in their community.

Local administration of the NYSCA program is usually carried out by parks and recreation personnel who have been trained by state coordinators of NYSCA to be facilitators. The national office of NYSCA provides all the training videos and printed materials to local chapters free of charge, and often the coach's membership fee is paid by the parks department or city government in recognition of the coach's commitment to the children of the community.

Table 2.—National Youth Sports Coaches Association (NYSCA) Code of Ethics Pledge

I hereby pledge to live up to my certification as a NYSCA coach by following the NYSCA Code of Ethics.

- I will place the emotional and physical well-being of my players ahead of any personal desire to win.
- I will remember to treat each player as an individual, remembering the large spread of emotional and physical development for the same age group.
- I will do my very best to provide a safe play situation for my players.
- I promise to review and practice the necessary first aid principles needed to treat injuries of my players.
- I will do my best to organize practices that are fun and challenging for all my players.
- I will lead, by example, in demonstrating fair play and sportsmanship to all my players.
- I will ensure that I am knowledgeable in the rules of each sport that I coach, and that I will teach these rules to my players.
- I will use those coaching techniques appropriate for each of the skills that I teach.
- I will remember that I am a youth coach, and that the game is for children and not adults.

Despite its economy, the NYSCA curriculum has limitations. The content areas presented during the 3- to 6-hour introductory sessions are limited in depth and are not suited to the needs of secondary school coaches. These areas are especially reduced because the curriculum has the additional agendas of avoidance of alcohol and other drugs and parent-coach interactions.

The Athletic Health Care System

The Athletic Health Care System (AHCS) was developed by Rice et al[16] as a model for providing comprehensive sports medicine services to high school athletes. Their premise was that neither coaches, athletes, nor their parents were prepared to anticipate or treat athletic injuries, and that preventable severe or even fatal injuries were regularly occurring in high school sports each year.

The AHCS, which has been adopted by more than 100 US high schools in nine states since its inception in 1978, is offered through the National Diffusion Network of the US Department of Education. The National Diffusion Network is a vehicle for the dissemination of exemplary, effective education programs throughout the country.

The assets of the AHCS are its methodical and comprehensive approach to assessing individual high schools' deficits in sports medicine services and developing an on-site infrastructure of personnel and protocol for the prevention and treatment of injuries.

The initial task of the AHCS is recruiting support from the school superintendent, high school principal(s), and athletic director. This support must be based on understanding the AHCS method, which is detailed, time-consuming, moderately expensive, and which requires enthusiastic cooperation from administration and athletic personnel throughout the needs-assessment, intervention, and follow-up periods. Clearly, the AHCS sets high standards for accountability in each school system and communicates that at the outset to coaches and administrators.

After conducting an assessment of current sports health care in each high school, complemented by an on-site visit by AHCS staff, a detailed report is drafted that identifies areas of potential remediation. During the assessment phase, a 30-hour course in the prevention and treatment of athletic injuries is taught by AHCS staff on-site to groups of 20 to 30 persons. This course is mandatory for all coaches and student trainers in the school system. The elements of the educational component provided by Rice and his staff include didactic sessions, hands-on experiences, a 340-page sports medicine syllabus authored by Rice, and a thorough grounding in the identification, documentation, and tracking of injuries—activities that are central to the accountability of the AHCS system. The curriculum does not address, however, coaching pedagogy or sports psychology. College credit is available for course attendance through the University of Washington (Seattle) Extension Division.

The AHCS encourages the development of a central training room in each high school and provides protocols and training for both coaches and student trainers in the appropriate stocking and use of the facility. The designated AHCS coordinator for each school is encouraged to attend the National Leadership Institute (Seattle, Wash) for 1 week, which augments that individual's skills in implementing the fundamentals of AHCS training in his or her school system.

The AHCS provides ongoing evaluation of the school system's athletic programs based on injury data kept by the coaching staff, behavioral observations of coaches by trained observers, and through two additional on-site visits by AHCS staff during the 18-month period following adoption of the program. Injury trend data by month and year, and compared with other school systems using the AHCS, is provided as part of this follow-up.

Compared with other coach-training methods detailed herein, the AHCS is time-consuming and costly (Table 3). To ensure uniformity in the system, the AHCS requires that *all* high school coaches participate in *all* aspects of training and follow-up. In addition, the breadth and complexity of the program mandates the administrative attention of a school coordinator dedicated to the goals of the AHCS.

Coach Effectiveness Training

The Coach Effectiveness Training (CET) Program was initially developed by Smith et al[31] in the late 1970s. Using the sound principles of empiric-based research, they observed and interviewed Little League coaches and players and then developed behavioral guidelines for coaches. The investigators theorized that teaching these behaviors to coaches would maximize the positive impact that sports participation has on children and adolescents.

Based on these empiric data, the CET Program was developed and tested using 34 Little League coaches in the Seattle area. The authors compared on-the-field behavior differences between control and experimental coaches as well as differences in players' perceptions of coaching behaviors, players' attitudes, and self-esteem with experimental and control Little Leaguers. Smith et al[32] reported that their curriculum (described in detail below) resulted in significant observed differences in the use of positive reinforcement by experimental coaches. In addition, the players of these coaches rated them higher in the use of positive reinforcement, mistake-related encouragement,

Table 3.—Youth Sport Coaching Curricula

Curriculum	Audience	Content	Advanced Training Available	Demonstrated Effectiveness	Cost
American Coaching Effectiveness Program	Novice and experienced coaches, high school and community	Pedagogy, psychology, sports medicine	Yes	Unpublished (Burton et al.[30] 1987)	$25/person
Athletic Health Care System	High school athletic departments and coaches	Sports medicine	No	Yes (Rice et al,[16] 1985)	$5800/school system
National Youth Sport Coaches Association	Community coaches and parents	Pedagogy, psychology, substance abuse	Yes	No data	Free
Coach Effectiveness Training Program	Community coaches	Psychology	No	Yes (Smith et al,[32] 1979)	~$300/workshop

and technical instruction and lower in the use of punishment and punitive technical instruction than the controls' players. Despite the fact that the win-loss percentages of the two groups did not differ, the experimental players reported greater enjoyment of the season and valued their relationship with their coaches and the other players more highly than did the Little Leaguers who played for the control coaches. More important, for those players whose self-esteem was measured after the previous season, the reported self-esteem of children who played for trained coaches increased significantly during the season following the training period, while that of the control group decreased.

The authors replicated their study in 1989 using 18 Little League teams of 10- to 12-year-olds from the Seattle area and reported their results at the annual meeting of the Association for the Advancement of Applied Sport Psychology in October 1991. There were no direct observations of coaching behavior in this study. However, players again rated the trained coaches higher in positive coaching behaviors and expressed greater enjoyment after playing for them. Players with low self-esteem "exhibited a significant increase in general self-esteem over the course of the season whereas low-esteem children who played for the untrained coaches did not change."[33] In addition, experimental players described less anxiety associated with competition than did the controls.

In the past 12 years, Smoll and Smith have conducted more than 160 workshops in which more than 7600 coaches have been trained. During a 2 ½-hour session, the authors present and model the behavioral guidelines of the CET Program. This method is predicated on the theory that coaches have tremendous potential in influencing the lives of the athletes who play under them and that the medium within which they work should never be bounded by winning or losing. Success, according to the CET Program, is defined as maximum effort in the quest for athletic victory.

The specific behavioral guidelines of the CET Program involve techniques for increasing positive reinforcement, reacting to mistakes in a way that encourages, maintaining order and discipline, creating a positive learning atmosphere, and techniques of communicating effectively with athletes and their parents. The coaches are encouraged to self-monitor by filling out a form after each practice, which forces them to consider the frequency with which they practiced behaviors emphasized during the training.

Of the coach-training programs reviewed herein, the CET is the most convincingly documented program in theory and research-proven effectiveness. Similar to the AHCS, the CET Program guarantees quality instruction because the authors conduct each training session themselves. Each workshop costs approximately $300, and the printed materials that are provided at no cost to the coach are readable, practical, and model a respect and positive regard for the coach that he or she is expected to imitate on the field. Despite its brevity and narrow scope, the CET Program clearly provides a dependable positive outcome at low cost for the sports system that sponsors it.

COMMENT

Clearly, coaches have the potential to influence in a positive way the lives of the many student athletes they encounter. Equally obvious is the fact that few coaches are required or even encouraged to acquire the skills that will ensure that athletes will compete safely and flourish emotionally under their tutelage. There exist several curricula, notably the ACEP, the AHCS, the curriculum of the NYSCA, and the CET Program, that provide a range of training and support sufficient to satisfy the needs of most community or school-based athletic programs. Failure to recognize the need to adopt minimum standards of training and support for coaches in these settings exposes the community, the school system, and the athlete to unnecessary risk and limits the wide-ranging benefits that athletic participation can provide children and adolescents.

RECOMMENDATIONS

Each state *must* establish minimum certification requirements for those who coach in the school setting. This might involve the endorsement of a specific core curriculum and would necessitate state-level administrative and financial support to individual school systems.

There appear to be multiple avenues for health care providers to take in advocating quality sports and quality coaches. We recommend one or more of the following actions: (1) If you choose to become a coach, choose to be a role model for other coaches by insisting that you be trained to do the job correctly. (2) Ask your local parks and recreation department if there are coaching standards for your community and assist in developing them if they do not exist. (3) Use local parent-teacher associations or school boards as a platform from which to advocate adequate credentials and continuing education for coaches as well as for minimum sports medicine services for student athletes. (4) Many states have health, physical education, recreation, and dance organizations that number coaches, athletic directors, health educators, and academicians among their members. Work with them to develop state standards and training opportunities.

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For more information on the coaching curricula, write or call National Youth Sports Coaches Association (NYSCA), 2611 Old Okeechobee Rd, West Palm Beach, FL 33409, 407-684-1141; American Coaching Effectiveness Program (ACEP), Human Kinetics Publishers Inc, Box 5076, Champaign, IL 61820, 800-747-4457; Athletic Health Care System (AHCS), Stephen G. Rice, MD, Division of Sports Medicine GB-15, University of Washington, Seattle, WA 98195, 206-543-1550; and Coach Effective Training (CET), Frank L. Smoll, Department of Psychology, Guthrie Hall, N1-25, University of Washington, Seattle, WA 98195, 206-543-4612.

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Cognitive and Motor Development in Infants at Risk for Human Immunodeficiency Virus

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• To evaluate the natural course of cognitive and motor development among infants infected with human immunodeficiency virus from birth, the Bayley Scales of Infant Development were administered to 96 infants between 5.5 and 24 months of age. Infants were divided into three groups on the basis of subsequent assessment of human immunodeficiency virus serologic status: seronegative (N = 45), seropositive (N = 12), and seroreverter (N = 39). Groups did not differ in race, infant age at initial testing, maternal age, maternal education level, maternal history of intravenous drug abuse, or percentage of children in foster care placement. Significant group differences were found on the Mental Development Index and Psychomotor Development Index, with the seropositive infants scoring significantly lower than the seronegative or seroreverter infants.

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The National Academy of Sciences projected a 10-fold increase in the number of cases of pediatric acquired immunodeficiency syndrome (AIDS) from 1986 to 1991, with most of these cases due to perinatal transmission. An estimated 10 000 additional children were predicted to be infected with human immunodeficiency virus (HIV) but not diagnosed with AIDS by the end of 1991.[1] Furthermore, the most recent data from the Centers for Disease Control[2] indicated that perinatal transmission was responsible for a larger increase (38%) in cases of AIDS between 1988 and 1989 than any other form of transmission. Because of the increasing prevalence of HIV infection in infants and children, it is particularly important that the developmental deficits related to HIV infection be documented. Johnson et al[3] noted that the lack of prospective data regarding the natural course and outcome of HIV infection in infants complicates appropriate health planning and counseling for these children and their families.

Review of the literature indicates significant developmental delays in the majority of children with HIV infection who have opportunistic infections (ie, diagnosed as having AIDS) or immunosuppression without opportunistic infections (ie, diagnosed as having AIDS-related complex).[4-12] In general, delays are more common in the areas of psychomotor skills, visuomotor integration, and visuospatial perception than in language or verbally mediated skills.[8-10,12] Regression in development is observed in many (but not all) children with AIDS and is perhaps somewhat less common in children with AIDS-related complex.[8,9] Only a few studies have assessed development of children who are seropositive for HIV but asymptomatic. In general, some developmental delay is observed in these children, compared with seronegative children from similar backgrounds.[3,12-15] It is not clear whether language or motor skills are more involved in the asymptomatic children.

Some investigators[16,17] have observed that children who are at high risk for HIV infection are often also at risk for psychosocial factors that may contribute adversely to cognitive development. These factors include maternal drug abuse during the prenatal period, lack of proper prenatal care that may be associated with low birth weight or prematurity, repeated periods of hospitalization and separation from the family, erratic caregiving in disturbed home environments, and lack of normal interaction with peers due to infectious disease precautions. The American Psychological Association Task Force on Pediatric AIDS calls for research to verify the nature and extent of developmental difficulties, as well as the relative effects of other confounding factors.[17] The current study was designed to evaluate, in a way that controls for as many prenatal and psychosocial factors as possible, the natural course of cognitive and motor development among infants who are infected with HIV from birth.

PATIENTS AND METHODS

Enrollment

Infants born to women at risk for HIV infection from August 1, 1988, to April 1, 1991, were identified and recruited for study from a full-term newborn nursery at a large inner-city hospital. Maternal HIV risk status was determined by a standardized screening questionnaire administered during a prenatal or postpartum interview and was defined as a history of intravenous drug use, prostitution, or sexual contact with an intravenous drug user or bisexual man. All women were offered HIV antibody testing after appropriate counseling. Additionally,

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Table 1.—Sociodemographic Characteristics of the Sample*

Characteristic	Group 1 (HIV Negative)	Group 2 (HIV Positive)	Group 3 (Seroreverters)	Total
Race, No. (%) B	42/45 (93.3)	11/12 (91.7)	37/39 (94.9)	**90/96** (93.8)
Sex, No. (%) M	24/45 (53.3)	7/12 (58.3)	16/39 (41.0)	**47/96** (49.0)
Mean age at examination, mo	10.2	10.2	9.5	9.9
Mean maternal age, y	25.7	25.2	26.3	25.9
Maternal education, No. (%)				
<HS	27/43 (62.8)	8/12 (66.7)	20/36 (55.5)	**55/91** (60.4)
HS graduate	10/43 (23.2)	1/12 (8.3)	14/36 (38.9)	**25/91** (27.5)
>HS	6/43 (14.0)	3/12 (25.0)	2/36 (5.5)	**11/91** (12.1)
Unknown	2	0	3	**5**
Foster care placement, No. (%) yes	15/45 (33.3)	4/12 (33.3)	8/39 (20.5)	**27/96** (28.1)
Child protective service referral, No. (%) yes	31/45 (68.9)	7/12 (58.3)	17/39 (43.6)	**55/96** (57.3)
Maternal history of IV drug use, No. (%) yes	39/45 (86.7)	8/12 (66.7)	27/39 (69.2)	**74/96** (77.1)
Maternal drug use during pregnancy No. (%) yes†	41/45 91.1)	8/12 (66.7)	21/38 (55.3)	**70/95** (73.7)
Unknown, No.	0	0	1	**1**

*HIV indicates human immunodeficiency virus; HS, high school; and IV, intravenous.
†$P<.001$.

urine toxicologic screens for illicit drug use, performed on urine obtained from the mother prenatally and/or at delivery, identified women who failed to report drug use when interviewed.

Excluded were infants who weighed less than 1500 g at birth, those who were of less than 34 weeks' gestation, and infants requiring admission to the neonatal intensive care unit for longer than 24 hours.

Approval for the study was obtained from the Joint Committee on Clinical Investigation of The Johns Hopkins Medical Institutions, Baltimore, Md. Informed consent was obtained both for participation in the study and for HIV antibody testing in the infant. Before discharge from the nursery, the infant's blood was tested for HIV antibody, and both maternal and infant medical records were reviewed.

Infants were then enrolled and observed during a 24-month period during clinic and home visits. Monthly to bimonthly clinic visits were scheduled for each infant. The HIV serologic status was tested at least every 6 months in those infants who were brought for their clinic appointments (at birth and 6, 12, 18, and 24 months). A more comprehensive assessment, including measurement of T-cell subsets and quantitative immunoglobulins, was carried out for those infants suspected to be HIV infected. Infants were assigned to one of three groups during the follow-up on the basis of HIV serostatus: (1) HIV seronegative (born HIV seronegative and remained seronegative), (2) HIV seropositive (born HIV seropositive and remained seropositive, with further evaluation confirming the presence of HIV infection), and (3) seroreverter (born HIV seropositive and became HIV seronegative by 15 months of age). Group 2 infants were classified according to severity of HIV symptoms by means of a system standardized by the Centers for Disease Control.[18] Classification was done by a pediatrician (N.H.) who was unaware of developmental test results. Infants in the P-0 class were asymptomatic and of unknown infection status; P-1 infants were asymptomatic but known to be infected; P-2A infants had generalized lymphadenopathy and hepatosplenomegaly; P-2AF infants exhibited P-2A symptoms plus dermatologic disease believed to be secondary to HIV infection; and P-2AD3F infants exhibited P-2AF symptoms plus chronic oral candidiasis. None of the infected infants had AIDS at the time of their developmental testing.

During the period from August 1, 1988, to April 1, 1991, a total of 178 infants born to mothers at risk for HIV infection were identified as eligible for the study. Permission was obtained from 171 (96%) of the mothers. Ninety-nine (58%) of these infants were born to HIV-seropositive mothers. Only 10 infant-mother pairs (6%) (three infants born to HIV-seropositive women) became unavailable for follow-up, including five infants who moved out of the area.

Developmental Assessment

Developmental testing, using the Bayley Scales of Infant Development, was scheduled to be conducted at the beginning of the 6-, 12-, 18-, and 24-month clinic visits. The assessments were conducted by a licensed psychologist (E.H.A.) who was experienced in dealing with infants and preschool children. She was unaware of the HIV status of the infants. Of the 171 infants, 101 were tested at least once. Due to erratic clinic visits, the first developmental testing did not occur until after 12 months of age for 24 of the 101 infants. All infants received initial testing by 24 months. None of the infants included in this analysis were treated with zidovudine before their initial developmental testing. Furthermore, five tested infants whose HIV status was indeterminate (P-0) were omitted from the current analysis because their infection status remained uncertain.

The remaining 96 infants were classified as follows: group 1 (HIV seronegative), 46.9% (45/96); group 2 (HIV seropositive), 12.5% (12/96); and group 3 (seroreverters), 40.6% (39/96). Demographic information on these 96 infants is presented in Table 1. Table 2 gives information regarding symptom severity among the 12 seropositive infants on the day of developmental testing.

RESULTS

The three groups (seropositive, seroreverters, and seronegative controls) did not differ in race ($P=.91$), sex ($P=.42$), infant age at initial testing ($P=.79$), maternal age ($P=.73$), maternal education ($P=.20$), maternal history of intravenous drug abuse ($P=.11$), or foster care placement ($P=.39$) (Table 1).

Groups differed significantly on maternal drug use during pregnancy ($P=.0009$), with greater use among mothers of HIV-seronegative infants than among mothers of the seropositive or seroreverter infants (Table 1). This is most likely related to recruitment procedures. Most HIV-seronegative women were identified due to intravenous drug usage and were less likely than HIV-seropositive women to report sexual contact with an HIV-risk contact. Primarily because of concerns regarding drug use among mothers, more of the seronegative children than seropositive or seroreverter infants had been

Table 2.—Characteristics of the 12 HIV-Positive Infants at Time of Developmental Testing*

Patient	Age at Examination, mo	PDI Score	MDI Score	CDC CLASS†
1	5.5	99	108	P-0
2	8.0	73	89	P-0
3	5.8	104	98	P-2A
4	6.5	80	88	P-2A
5	8.0	110	101	P-2A
6	8.9	50	69	P-2A
7	14.0	103	88	P-2A
8	15.0	73	92	P-2A
9	6.0	83	52	P-2AF
10	6.0	104	110	P-2AF
11	19.0	80	56	P-2AF
12	19.0	96	99	P-2AD3F

*HIV indicates human immunodeficiency virus; PDI, Psychomotor Development Index; MDI, Mental Development Index; and CDC, Centers for Disease Control.

†P-0 indicates asymptomatic, infection status unknown (infection status subsequently determined to be positive for the P-0 infants in this study); P-2A, generalized lymphadenopathy and hepatosplenomegaly; P-2AF, P-2A symptoms plus dermatologic disease believed to be secondary to HIV infection; and P-2AD3F, P-2AF symptoms plus chronic oral candidiasis.

Table 3.—Mental Development Index Scores for Seronegative, Seropositive, and Seroreverter Infants

Score	Seronegative, No. (N=45)	Seropositive (N=12) No.	Seropositive (N=12) Severity Status*	Seroreverter, No. (N=39)
≥130	0	0	. . .	1
125-129	0	0	. . .	0
120-124	4	0	. . .	0
115-119	5	0	. . .	6
110-114	5	1	P-2AF	2
105-109	5	2	P-0, P-2AD3F	2
100-104	3	1	P-2A	6
95-99	5	1	P-2A	8
90-94	6	1	P-2A	7
85-89	5	3	P-2A, P-2A, P-0	1
80-84	3	0	. . .	4
75-79	1	0	. . .	1
70-74	1	0	. . .	1
65-69	1	1	P-2A	0
60-64	1	0	. . .	0
55-59	0	1	P-2AF	0
50-54	0	1	P-2AF	0

*See Table 2 for explanation.

Table 4.—Psychomotor Development Index Scores for Seronegative, Seropositive, and Seroreverter Infants

Score	Seronegative, No. (N=43)	Seropositive (N=12) No.	Seropositive (N=12) Severity Status*	Seroreverter, No. (N=38)
130-134	1	0	. . .	0
125-129	2	0	. . .	3
120-124	3	0	. . .	2
115-119	3	0	. . .	5
110-114	6	1	P-2A	7
105-109	4	0	. . .	4
100-104	5	3	P-2A, P-2A, P-2AF	3
95-99	5	2	P-0, P-2AD3F	2
90-94	3	0	. . .	3
85-89	8	0	. . .	0
80-84	3	3	P-2A, P-2AF, P-2AF	4
75-79	0	0	. . .	2
70-74	0	2	P-0, P-2A	2
65-69	0	0	. . .	1
60-64	0	0	. . .	0
55-59	0	0	. . .	0
50-54	0	1	P-2A	0

*See Table 2 for explanation.

referred to child protective service, although this difference did not reach significance ($P = .065$).

When data for the seronegative and seroreverter infants were combined, forming a group of noninfected infants, there continued to be no significant group differences (between infected and noninfected infants) in infant age, race, sex, maternal age, maternal level of education, maternal history of intravenous drug abuse, foster care placement, or protective service involvement. Maternal drug abuse during pregnancy did not significantly differ between the infected (seropositive) and noninfected (seronegative plus seroreverter) groups.

Tables 3 and 4 give the scores on the Mental Development Index (MDI) and Psychomotor Development Index (PDI), respectively, for the infants in the three groups.

Analysis of variance revealed significant group differences in the MDI ($P = .035$). Post hoc analyses (least-squares differences technique) demonstrated that the seropositive infants scored significantly lower than the seronegative and seroreverter infants; no significant difference was found between the seronegative and seroreverter infants on the MDI (Table 5).

Group differences were also found on the PDI ($P = .014$). Post hoc analyses again revealed that the seropositive group scored significantly lower than the other two groups, with no significant difference between the seronegative and seroreverter infants (Table 5).

A repeated-measures analysis of variance revealed no significant interaction between cognitive domain (MDI vs PDI) and group ($P = .87$). Thus, the relationship between MDI and PDI scores was not different for the three groups.

Table 5.—Mean Score for Bayley Scales of Infant Development by Human Immunodeficiency Virus Group

	Seronegative (N=45)	Seropositive (N=12)	Seroreverter N=39)	F	*P*
Mental Development Index Score	99.6	87.5	99.9	3.47	.035
Psychomotor Development Index Score	102.7	87.9	102.1	4.46	.014
Mean age at testing, mo	10.2	10.2	9.5	0.24	NS*

*NS indicates not significant.

The MDI and PDI scores were compared for infants who had been exposed to substance abuse in utero and those who had not been exposed, independent of HIV status. The nonexposed group (n=25) had a mean MDI of 102.9 and a PDI of 108.8, while the exposed group (n=70) had a mean MDI of 96.6 and PDI of 98.9. The *t* tests revealed no significant group differences on MDI (P=.10). A significant difference was found for PDI (P=.002), with the exposed group performing significantly worse than the nonexposed group.

COMMENT

Assessment of HIV seropositive, seronegative, and seroreverter infants indicated significant developmental differences based on HIV status, both in cognitive and motor domains. As theorized by other investigators, these manifestations of encephalopathy are presumed to be due to primary and persistent infection of the nervous system with the HIV virus,[4,12] not simply the result of other nonneurologic symptoms (eg, recurrent bacterial infections) or environmental stressors (eg, repeated hospitalizations). As demonstrated in Tables 3 and 4, those seropositive infants with the lowest scores on developmental assessment are not necessarily those with the most severe and/or greatest number of nonneurologic symptoms. Most of the seropositive infants are functioning below the means of the seronegative and seroreverter groups. It must be noted, however, that many of the seropositive infants were still functioning within the normal range, with a few actually functioning above average. Again, however, those infants who were doing well developmentally were not necessarily those who were demonstrating the fewest and/or least severe symptoms of HIV disease. Findings of developmental delay before the onset of significant HIV symptoms are consistent with previous investigations.[3,12-15]

The lack of significant difference between the seronegative and seroreverter groups in MDI and PDI suggests that in utero exposure to HIV infection per se does not result in motor and cognitive delays, at least during infancy. Furthermore, the significant difference between the seroreverter and seropositive groups suggests that the delays observed in the seropositive infants were not simply the result of such factors as parental overprotectiveness or increased medical involvement, as presumably the seroreverter infants were treated similarly to the seropositive infants, at least until seroreversion occurred.

In general, investigations with more severely symptomatic infants (those with AIDS and AIDS-related complex) have found more delays in motor skills, perceptuomotor skills, and visuospatial perceptual functioning than in verbally mediated skills.[8-10,12] One study[10] found no such pattern of delay in a group of noninfected children from similar sociocultural backgrounds. Some studies of HIV-seropositive children who were asymptomatic documented motor or perceptuomotor delay with little or no cognitive or language abnormalities,[3,12,15] whereas Nozyce et al[14] found that prelinguistic skills were more delayed than other areas of functioning. The current study did not provide evidence of significant difference in motor vs cognitive delays due to HIV infection in children who have relatively few symptoms.

One of the strengths of this study is the inclusion of a large control group of seronegative infants who were recruited from a population with social background similar to that of the seropositive infants. As indicated in Table 1, the seropositive, seroreverter, and seronegative infants were matched fairly well on age, sex, race, maternal age, maternal level of education, and percentage of children in foster care placement. The groups were less well matched on maternal history of intravenous drug use and percentage of children with protective service involvement, but the groups differed significantly only on maternal drug use during pregnancy. It is important to note that the seropositive infants were *less* likely to have been exposed to drugs prenatally than were the seronegative infants. Thus, the slower cognitive and motor development among the seropositive infants cannot be attributed to drug exposure.

Findings of the current study are limited by the small number of subjects in the HIV-seropositive group. Additional studies of larger numbers of HIV-seropositive children will be necessary to assess fully the broad range of developmental variations and abnormalities resulting from this disease.

An additional problem with this study involves the variability of age of initial developmental assessment. This was due to many caregivers' failure to comply with clinic appointments, despite efforts to remind them, provide transportation, and maintain contact, including through home visits. The difficulty in following up this sample is typical of studies involving inner-city substance-abusing populations.

Although previous research with more severely affected infants and children demonstrated significant cognitive and motor delays, this study demonstrated that delays can be observed in children who are less severely affected. As indicated in Table 2, the clinical manifestations of many of the HIV-infected infants were fairly mild, compared with those of children in previous studies.

In many of the HIV-infected infants, developmental delays were fairly subtle, with most MDI and PDI scores falling within the average to low-average range (80 to 110). If health professionals are not specifically attuned to these subtle differences, appropriate intervention may not be instituted as early as possible. With increased survival of HIV-infected children as a result of antiretroviral treatment, these subtle differences may progress to more obvious and disruptive delays as the children get older. Health care providers should be aware of these differences and advocate the development of appropriate educational and rehabilitative services that will be needed for these children.

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Prevention

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue

To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS

None known.

WARNINGS

SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS

General

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Reproduction studies in animals have not been completed. Mutagenicity studies were negative. Carcinogenicity studies have not been performed with SURVANTA.

ADVERSE REACTIONS

The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, transient bradycardia occurred with 11.9% of *doses*. Oxygen desaturation occurred with 9.8% of *doses*.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

	All Controlled Studies		
Concurrent Event	**SURVANTA (%)**	**Control (%)**	***P*-Value[a]**
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a] *P*-value comparing groups in controlled studies

rhage, however, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% *v* 30.8%, $P = 0.001$; and 48.8% *v* 34.2%, $P = 0.047$, respectively). The rate in a Treatment IND involving approximately 4400 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 3700 pretreatment and post-treatment serum samples were tested by Western Blot immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardio-respiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal: renal failure, hematuria.

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures.

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia.

Systemic: fever, deterioration.

Follow-Up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies

Six-month adjusted age follow-up evaluations have not been completed. Preliminarily, in 605 (333 treated) of 916 surviving infants, there are trends for decreased cerebral palsy and need for supplemental oxygen in SURVANTA infants. Wheezing at the time of examination tended to be more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Twelve-month follow-up data from the multiple-dose studies have been completed in 328 (171 treated) of 909 surviving infants. To date no significant differences between treatments have been found, although there is a trend toward less wheezing in SURVANTA infants in contrast to the six month results.

OVERDOSAGE

Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED

SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 8 mL of SURVANTA (NDC 0074-1040-08). Each milliliter contains 25 mg of phospholipids (200 mg phospholipids/8 mL) suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

June, 1991

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Asymmetric Septal Hypertrophy in Infants of Diabetic Mothers

Fetal Echocardiography and the Impact of Maternal Diabetic Control

Michael J. Cooper, MD; Marlene A. Enderlein; Harold Tarnoff, MD; Claude L. Rogé, MD

• Maternal hyperglycemia may result in fetal hyperinsulinemia and asymmetric septal hypertrophy, macrosomia, and hypoglycemia in infants of diabetic mothers. We monitored glycosylated hemoglobin levels in 61 pregnant diabetic women each trimester as an index of maternal glycemic control and did serial fetal echocardiograms starting at 18 weeks of gestation. At delivery, cord blood C-peptide levels were obtained as an index of fetal hyperinsulinemia. Infants were assessed for hypoglycemia, macrosomia and septal thickening by echocardiography. Nineteen of the 61 infants (31%) had septal hypertrophy, were heavier, and had higher cord blood C-peptide levels and lower serum glucose levels than unaffected infants. Maternal glycosylated hemoglobin levels were higher during the third trimester in mothers of affected infants. Our data support a possible relationship between third-trimester maternal hyperglycemia and neonatal asymmetric septal hypertrophy, macrosomia, and hypoglycemia.

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Transient asymmetric septal hypertrophy (ASH) in infants of diabetic mothers (IDMs) has been well documented since its initial description in 1976.[1] According to some authors, fetal hyperinsulinism triggered by passive placental transfer of maternal glucose leads to ASH, as well as neonatal macrosomia and hypoglycemia, in these infants.[2-7] Others have not found a clear connection between these neonatal findings and the quality of maternal diabetic control.[8,9]

The purpose of this investigation was to monitor IDMs and their mothers prenatally and postnatally to determine the time of onset of increased septal thickness in gestation and the presence and degree of ASH in the neonate relative to the quality of maternal diabetic control and to evidence of neonatal hyperinsulinemia.

SUBJECTS AND METHODS

Seventy-one pregnant diabetic women were referred by their attending obstetricians to the pediatric cardiology divisions of Kaiser Permanente Medical Centers within Northern California and consecutively enrolled in the study. The procedure was approved by the Institutional Review Board of the Kaiser Permanente Medical Care Program, Northern California Region, and each woman gave informed consent for inclusion in the study. Initial referral was generally at 18 to 22 weeks of gestation. Sixty-one women completed follow-up to delivery at or beyond the 36th week. All but five were insulin dependent; 22 had gestational diabetes and 39 were permanent diabetics. Ten diabetic pregnant women were excluded from analysis because the women were unavailable for follow-up studies.

Maternal glycosylated hemoglobin (HbA_{1c}) levels, routinely obtained in the high-risk obstetric clinic once per trimester, were expressed as a percentage of total hemoglobin level as an index of the quality of maternal diabetic control during a period of several months. The $HbA1_c$ level was determined by means of a high-performance liquid chromatographic method at the Kaiser Permanente Northern California Regional Laboratory, Berkeley, Calif.[10] The laboratory has determined that a percentage of HbA_{1c} of up to 6.5% reflects adequate diabetic control and that inadequate control is reflected by values of 6.6% or greater. Because the test is accurate only with normal amounts of hemoglobin A, all women were screened for hemoglobinopathies, and none were found.

Fetal echocardiograms were done starting at about the 18th week of gestation and were repeated every 4 to 8 weeks to evaluate intracardiac anatomy and measure ventricular-wall thickness. Studies were performed with one of two scanners (Advanced Technology Laboratories Ultramark 8 sector scanner, Advanced Technology Laboratories, Bothell, Wash; or Hewlett Packard 500G, Hewlett Packard, Mountain View, Calif) using a 3.5-mHz transducer. M-mode tracings were recorded at 50 mm/second with a page printer or a black-and-white stripchart recorder. The M-mode measurements of ventricular-wall thickness were obtained from a four-chamber view (Fig 1) with the transducer perpendicular to the ventricular septum and the M-line directed through the ventricles immediately beneath the atrioventricular valves. Wall thicknesses were measured from the M-mode echocardiogram tracing to the nearest 0.5 mm with leading-edge methods, and averages were taken from a minimum of three cardiac cycles. All echocardiographic measurements were made by one of two experienced observers blinded to the quality of maternal diabetic control and to results of previous studies. Because fetal M-mode echocardiographic measurements have been shown to have a degree of precision similar to that reported for the adult heart, intraobserver reperformance reproducibility was not evaluated.[11] Echocardiograms were obtained in every newborn infant within a few days of delivery. Infants were determined as having ASH by fulfilling two criteria: absolute ventricular septal thickness of 5 mm or more and a ratio of the septal to left ventricular free-wall ratio of 1.3:1 or more. Of the 61 IDMs, 19 were found to have ASH; the other 42 made up the non-ASH group.

At delivery, mixed arteriovenous cord blood was collected and assayed for C-peptide as an index of fetal hyperinsulinemia. C-peptide is a cleavage product of proinsulin to insulin and is secreted by β cells in amounts equimolar with insulin. Its measurement in cord blood has been shown to reflect endogenous fetal levels of insulin.[12] Serum was separated and frozen at −30°C until assayed. Serum C-peptide level was measured by

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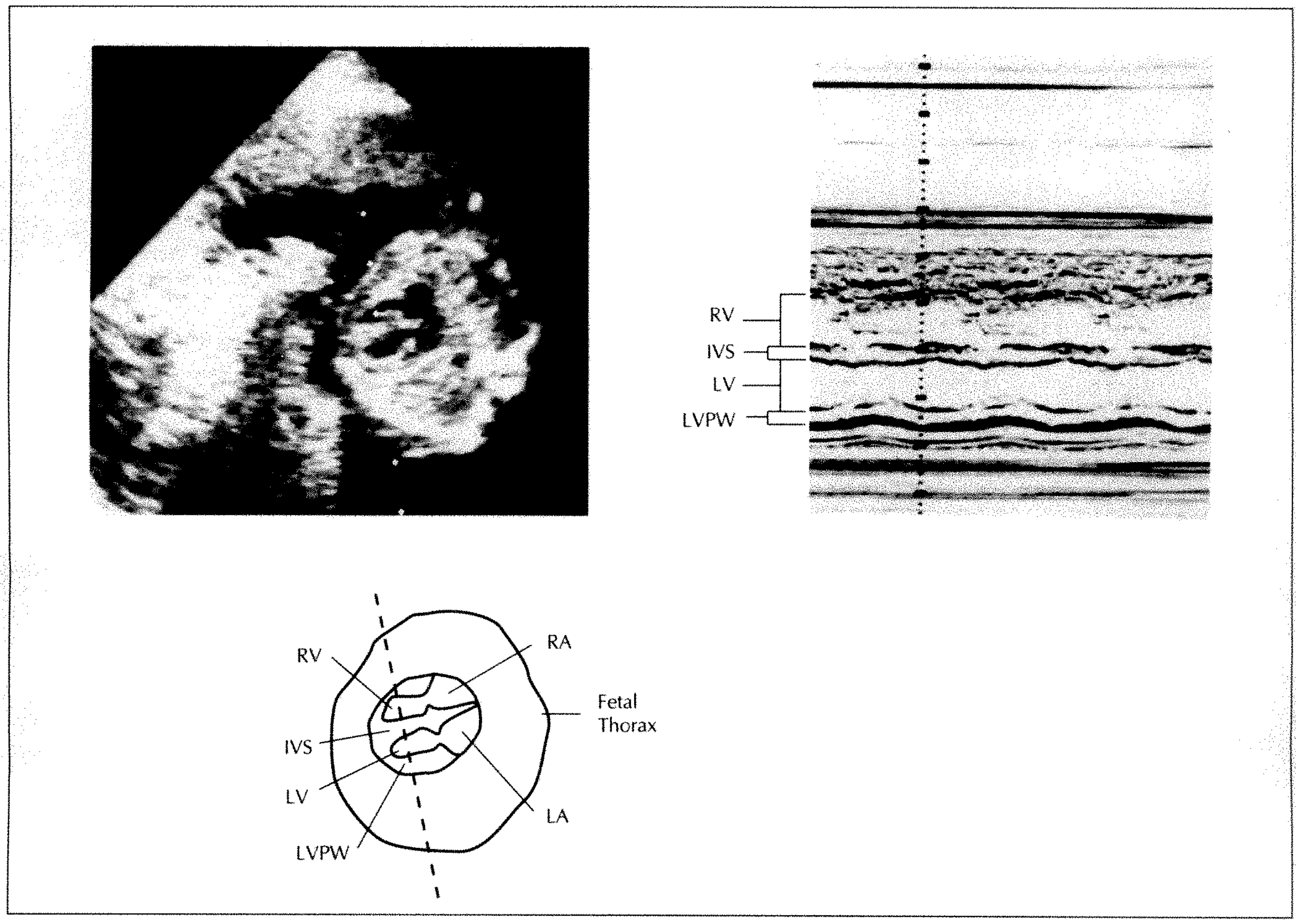

Fig 1.—*Fetal echocardiogram demonstrating four-chamber view (left, and illustrated schematically below) from which M-mode measurements were obtained (right). IVS indicates interventricular septum; LV, left ventricle; LVPW, left ventricular posterior wall; RV, right ventricle; LA, left atrium; and RA, right atrium.*

radioimmunoassay after precipitation of the antibody-proinsulin complex by glycol.[13]

Gestational age at birth was determined by prenatal verification of pregnancy dates and clinical assessment of the newborn. The diagnosis of respiratory distress was based on clinical signs, increased oxygen requirement, and radiologic findings.

Serum glucose level was monitored routinely in the intensive care unit starting within the 1st hour of life and continued for at least the first 24 hours, with the lowest value obtained by retrospective review as representing the presence or degree of hypoglycemia. Because intravenous glucose therapy was instituted in every infant with a blood glucose concentration of less than 1.7 mmol/L, this value is not a true nadir. Serum glucose was measured either by a chromogen strip test (Chemstrips b.G., Boehringer-Accuchek III, Boehringer Mannheim Diagnostics, Indianapolis, Ind) with a quantitative interpretation by reflectance meter at the bedside or by a serum glucose level determined in the laboratory by means of a glucose analyzer (Beckman Instruments Inc, Brea, Calif).

Statistical significance was determined by two-tailed Student's t test to compare group mean values; when the criteria for conducting the t test were not met, the nonparametric Wilcoxon Rank-Sum Test was applied to the data. The χ^2 test with Yates' correction for continuity was used to analyze contingency table data.

RESULTS

The presence of ASH was shown by echocardiography in 19 of the 61 IDMs, a prevalence of 31%. The infants with ASH had fetal echocardiograms with a significantly greater degree of mean ventricular septal thickness starting at 31 to 34 weeks of gestation (Fig 2). Before that point, their mean septal thickness did not differ significantly from those of fetuses who did not prove to have ASH at delivery.

We compared characteristics of the diabetic mothers of infants with and without ASH (Table 1). No statistically significant differences were noted in the type of maternal diabetes or the average daily insulin dose per kilogram in the third trimester. Maternal HbA_{1c} values as an index of the quality of maternal glycemic control in each trimester did not differ between the two groups during the first two trimesters, although a statistically significant difference was noted during the final trimester.

We also compared the IDMs with and without ASH (Table 2). There was no difference in the mean gestational age at birth. Babies with ASH were significantly heavier, had a significantly lower mean trough serum glucose level after birth, and had a significantly higher mean cord blood C-peptide level.

One infant had severe respiratory distress with clinical evidence of persistent pulmonary hypertension requiring ventilatory support. This 4.1-kg infant had marked ASH with a septal thickness of 9 mm. His mother had a third-trimester HbA_{1c} value of 9.4%.

Five (8.2%) of the 61 infants were noted before or at time of delivery to have structural heart defects. In three of the 42 infants without ASH, defects included atrioventricular canal defect in one, bicuspid aortic valve in one, and ven-

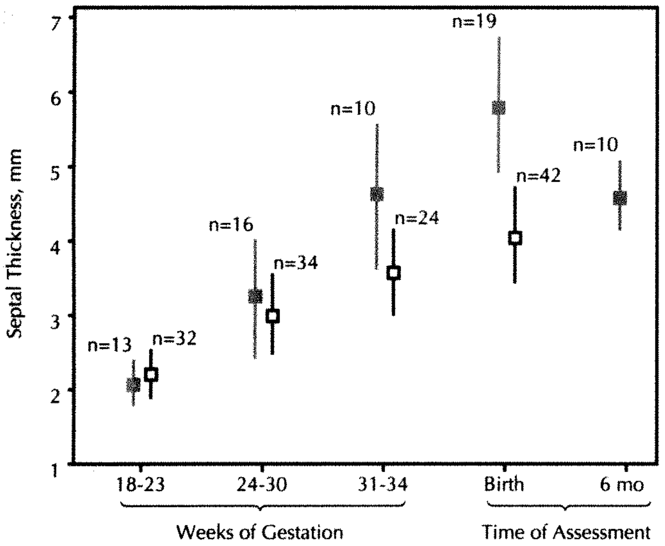

Fig 2.—*Septal thickness on serial fetal echocardiograms during gestation and at birth in infants of diabetic mothers born with asymmetric septal hypertrophy (closed squares) vs infants without asymmetric septal hypertrophy (open squares). Significant difference (P<.005) between the two groups was first noted at 31 to 34 weeks of gestation. For infants with asymmetric septal hypertrophy at birth, 6-month assessment of septal thickness is also shown (n indicates number of observations; variance bars, mean±1 SD).*

Table1.—Comparison of Mothers of Infants With and Without Asymmetric Septal Hypertrophy (ASH)

	ASH	Non-ASH	P
Type of diabetes, No.*			
Preexisting diabetes mellitus	14	25	NS†
Gestational	5	17	NS
Insulin, U/kg (mean ± SD)	0.7 ± 0.4 (n = 19)	0.9 ± 0.5 (n = 42)	NS
% glycosylated hemoglobin (mean ± SD)			
1st trimester	7.0 ± 1.5 (n = 15)	7.0 ± 1.5 (n = 34)	NS
2nd trimester	6.1 ± 1.4 (n = 13)	5.9 ± 0.8 (n = 30)	NS
3rd trimester	6.7 ± 1.8 (n = 16)	5.7 ± 0.9 (n = 31)	.01

*By χ^2.
†NS indicates not significant.

tricular septal defect in another. Atrial septal defect was found in two of the 19 infants with ASH. Although we noted no difference in the prevalence of heart defects in infants with and without ASH or in relation to the quality of maternal diabetic control in any trimester, the small number of cases makes conclusions about significant or nonsignificant correlations impossible.

COMMENT

In reports published in the early 1940s, Miller and Wilson[14,15] described cardiac hypertrophy and hyperplasia of the pancreatic islands of Langerhans in macrosomic IDMs who were either stillborn or who died during the first few days of life. With the advent of echocardiography in the mid-1970s, this cardiac hypertrophy in IDMs was more precisely defined as involving a "transient hypertrophic subaortic stenosis."[1]

Table 2.—Comparison of Infants of Diabetic Mothers With and Without Asymmetric Septal Hypertrophy (ASH)

	Mean ± SD		
	ASH	Non-ASH	P
Gestational age, wk*	38.2 ± 1.2 (n = 19)	38.1 ± 1.4 (n = 42)	NS†
Birth weight, g*	4009 ± 721 (n = 19)	3457 ± 645 (n = 42)	<.01
Trough serum glucose, mmol/L‡	2.3 ± 1.4 (n = 18)	3.3 ± 1.4 (n = 36)	<.01
Cord blood C-peptide, mmol/L‡	1.26 ± 0.79 (n = 6)	0.53 ± 0.30 (n = 12)	<.05

*By *t* test.
†NS indicates not significant.
‡By Wilcoxon sign-rank test.

Subsequent reports have further characterized the prevalence in IDMs of this generally asymptomatic ASH at about 30% and have documented its resolution by about the age of 1 year.[1,3,6,7,16-18] The association between presence and degree of ASH in the IDM and quality of maternal glycemic control has not been clearly defined.

Pedersen[2] in 1954 suggested that poorly controlled maternal diabetes mellitus with chronic maternal hyperglycemia passively produces fetal hyperglycemia, which induces fetal hyperinsulinemia. Fetal hyperinsulinemia, previously implied by the presence of pancreatic β-cell hyperplasia in these infants,[2,14,15] has more recently been documented by a method based on high-performance liquid chromatography.[19] Cord C-peptide levels reflecting endogenous fetal levels of insulin have been correlated with neonatal hypoglycemia and macrosomia in IDMs.[12] Insulin stimulates growth in the third-trimester fetus by regulating glycogen, fat, and protein synthesis.[20] The normal degree of accelerated weight gain during the third trimester is apparently exaggerated in the hyperinsulinemic fetus, with resultant neonatal macrosomia. The neonatal heart has been shown to be rich in insulin receptors,[21] and it has been suggested that the mild, disproportionate ventricular septal thickening seen in the normal fetus[22,23] is exaggerated in the hyperinsulinemic third-trimester fetus, giving the appearance of ASH in the IDM. Although the gross morphologic and echocardiographic appearance of this ASH is somewhat similar to that of the autosomal dominant progressive type, which is rarely seen in infants,[24,25] the conditions are completely unrelated. In ASH of the IDM, there is no histologic evidence of myocardial cellular disarray,[6,16,25] the condition rarely causes any clinically significant left-ventricular outflow obstruction,[1,16,18] and it spontaneously resolves within the first year of life.[1,3,6,7,16-18] While our findings and those of other authors support an association between poor maternal glycemic control and evidence of fetal hyperinsulinemia and ASH in the IDM,[2-7,12] others have failed to demonstrate any such correlation.[8,9]

The present study is an attempt to evaluate each step of Pedersen's[2] hypothesis in a large group of pregnant diabetics: serial HbA_{1c} levels in each trimester of pregnancy provided an index of the quality of maternal glycemic control; fetal insulin levels were reflected by cord C-peptide determination at birth; and infants were examined for some of the potential consequences of fetal hyperinsulinemia, as reflected by the presence and degree of ASH, macrosomia, and hypoglycemia. Evaluation of the prevalence and degree of hypoglycemia in the newborns was hampered by the need for therapeutic intervention and because we relied on values derived from either a bedside semiquantitative chromogen test strip or from the laboratory glucose analyzer. Although this is common practice in neonatal intensive care units, rapid semiquantitative methods are of questionable validity.[26] Furthermore, a recent study by Menon et al[19] pointed to the biologic activity of antibody-bound insulin transferred from the mother treated with insulin to the fetus. Thus, in addition to the effect of fetal hyperinsulinemia generated by poor maternal control, those well-controlled insulin-dependent mothers with high levels of anti-insulin antibody may also be at risk for giving birth to infants with macrosomia and the other complications of IDMs. The authors suggest that insulin of the lowest immunogenicity be used in treating pregnant diabetic women. Nevertheless, our results appear to support Pedersen's hypothesis and point to the importance of adequate maternal glycemic control, especially in the third trimester of pregnancy.

Although there are isolated case reports concerning the time of onset of ASH during fetal life,[27] we have shown that for the population of infants found to have ASH at birth, fetal echocardiography detected septal thickening at 31 to 34 weeks of gestation. At this point in gestation, the fetuses showed a significant increase in septal thickness distinct from those who did not prove to have ASH at birth whose septal thickness was in keeping with reported normal fetal measurements.[23] Prenatal detection of ASH at this point in gestation might have clinical relevance insofar as persistent pulmonary hypertension of the newborn and idiopathic respiratory distress syndrome have been reported in IDMs with ASH.[5-7,9,14,16,17] In our study of fairly well-controlled pregnant diabetic women, this complication occurred in only one infant, who had severe ASH and was born to a mother with extremely poor third-trimester glycemic control. Arranging for the delivery for a pregnant patient with poorly controlled diabetes at a site where neonatal intensive care is available might thus be appropriate if a late-gestation fetal echocardiogram shows significant ASH.

These findings suggest that in pregnancies of diabetic patients, adequate control of maternal blood glucose levels, especially in the third trimester, may decrease the presence and degree of neonatal hypoglycemia, macrosomia, and ASH. We further speculate that high maternal HbA_{1c} levels during the third trimester and fetal echocardiographic evidence of significant ASH might serve as useful markers in identifying infants at risk for developing potentially significant complications and warrant their delivery at a site where appropriate intensive neonatal care can be provided.

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Ultrasound Screening of High-Risk Infants

A Method to Increase Early Detection of Congenital Dysplasia of the Hip

Robert S. Walter, MD; James S. Donaldson, MD; Cheryl L. Davis, MD; Arnold Shkolnik, MD; Helen J. Binns, MD; Norris C. Carroll, MD; Robert T. Brouillette, MD

• Congenital dysplasia of the hip (CDH) continues to be missed by routine physical screening examinations in the early months when treatment is most effective. Real-time ultrasonography (US) is valuable in the detection of CDH in the young infant. We performed a prospective study to evaluate one US screening strategy that targets a select "high-risk newborn" population at risk for CDH aiming to increase the early diagnosis of this condition. From 1772 consecutive births at one hospital, we identified 97 (5.5%) newborns with risk factors for CDH: breech delivery, 73 babies; family history, 26 babies; postural abnormalities, five babies; and oligohydramnios, four babies. Eleven newborns had two risk factors. We studied 69 of these newborns with US. There were four cases of CDH in this group. Three of these babies had completely normal pediatric physical examination results at the time of the US study (at 14, 75, and 100 days, respectively) despite dysplasia diagnosed by US. All were successfully treated with a harness as outpatients. We conclude that a screening program entailing identification and subsequent US of the hip of newborns with specific physical and historical risk factors for CDH increases early diagnosis. Further analysis suggests this approach is cost-effective.

(*AJDC.* 1992;146:230-234)

Congenital dysplasia of the hip (CDH) (or developmental dysplasia of the hip) represents a spectrum of disease from total dislocation to partial dislocation or subluxation. The incidence of CDH is estimated at 4 per 1000 births (two completely dislocated and two with subluxation).[1] It is well established that in treating CDH, early diagnosis improves outcome.[2] If CDH is detected in the first months of life, outpatient treatment with a soft harness is safe, inexpensive, and effective.[3] However, delay in the diagnosis of CDH often necessitates inpatient traction and casting or operative intervention, often with a suboptimal outcome.[4,5] The physical, emotional, and medical costs of delayed diagnosis of CDH are enormous for the child and parents and are also responsible for large pediatric malpractice payments.[6] In addition, up to 25% of adult hip osteoarthritis requiring surgery has been attributed to the late effects of mild CDH.[7]

The introduction of the Ortolani and Barlow maneuvers increased early detection of CDH, causing a decrease in the incidence of late CDH in the 1950s and 1960s.[5,8] Unfortunately, in recent years the incidence of late CDH has reached a plateau and cases continue to be missed until late infancy. Up to 50% of CDH is undetected at pediatric neonatal examination[4,9,10] and missed by orthopedic surgeons.[11,12] Some authors have suggested that the physical examination may actually stretch the capsule and cause some cases of dysplasia.[13] Thus, improved methods of increasing early diagnosis are needed.

Ultrasonography (US) of the infant hip, pioneered by Reinhard Graf,[14,15] has proved valuable in CDH due to its high accuracy and low risk in infants.[16-19] However, nonselective screening strategies that have used US of the hip for all newborns in the first week of life have resulted in high treatment rates (potential false positives, due to lower specificity of US of the hip in the neonate) and are costly.[17,20-22]

Certain historical and physical factors are known to increase the risk of CDH. In large series of patients treated for CDH, breech presentation was seen in 15% to 30%[3,4,8,23,24] and a positive family history was seen in 8% to 33%.[25-27] Postural abnormalities and oligohydramnios are also known risk factors.[4,28] In all, approximately 30% to 50% of children with CDH were "high-risk newborns" with one of the above risk factors. We therefore designed a prospective study to test the hypothesis that selective US screening of high-risk infants outside the newborn period would increase the early detection of CDH and be cost-effective.

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Ultrasound (US) Classification*

Ultrasound Type	Recommendation
Normal	Follow-up clinically†
Immature <3 mo‡ vs borderline abnormal >3 mo	Follow-up US 4-8 wk†
Mild dysplasia	Refer for treatment
Severe dysplasia	Refer for treatment

*Revised from Graf.[15]
†Assumes physical examination shows stable hip.
‡Deficient bony acetabulum: immature <3 months; borderline abnormal >3 months.

PATIENTS AND METHODS

From October 1, 1987, to March 15, 1988, we prospectively screened all liveborn deliveries at the Prentice Women's Hospital (Chicago, Ill), a large perinatal referral center, using hospital database and chart records. Targeted newborns considered to be at high risk for CDH included those with at least one of the following: breech presentation (frank, footling, complete); family history of CDH (primary—sibling or parent; secondary—aunt/uncle or cousin); congenital postural abnormality (scoliosis, metatarsus varus, torticollis, talipes equinovarus); or oligohydramnios. Newborns who had been less than 36 weeks' gestation, had teratologic or myelodysplastic dislocations, had chromosomal abnormalities, or had been admitted to the intensive care unit for longer than 1 day were excluded.

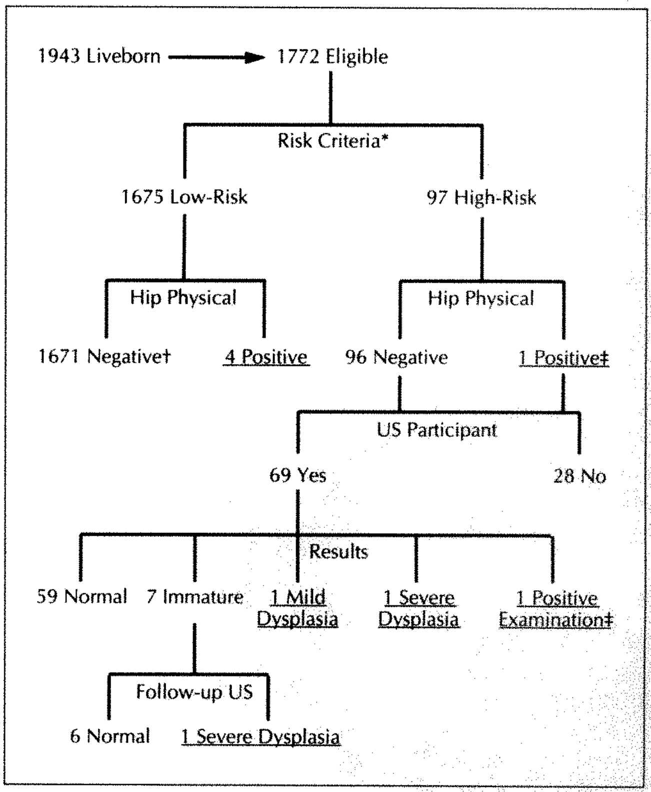
All eligible infants were included in the hospital computerized review of fetal monitoring records for identification of breech presentation or oligohydramnios. A family history of CDH was elicited with an obstetric recovery room questionnaire. Postural abnormalities were identified at newborn examinations performed on all eligible infants, which included testing for hip instability. The birth records and questionnaires were reviewed weekly. The parents and pediatricians of all newborns who were high risk for CDH were contacted in the newborn's first month and invited to participate in the study. Signed informed consent was obtained from the parents at the time of US study. This investigation was approved by the appropriate institutional review boards.

All US examinations of the hip on high-risk infants were performed before 3 months of age by pediatric radiologists (J.S.D., A.S.)with extensive experience in US of the hip at Children's Memorial Hospital, Chicago, Ill. All ultrasonographers were "blinded" as to the physical findings and specific history. All US examinations were performed with equipment (Acuson 128, Mountain View, Calif) using a linear array 5.0-MHz transducer to image the hip in the coronal plane. Evaluations were based on the Graf[15] classification that includes both subjective and objective analysis. Recommendations were based on the US findings in the most severely affected of the two hips (Table). A clinical hip examination was performed by a single pediatrician (R.S.W.) before each US study.

Infants with an unstable hip on clinical examination at any time during the study were referred to an orthopedic surgeon through their pediatrician regardless of US findings. All treatment decisions were made by the private pediatricians, parents, and their chosen orthopedic consultants. The ordering of a plain hip roentgenogram was at the discretion of the orthopedic consultant.

Pertinent historical, birth, and physical data were recorded on all eligible newborns. Separate data files on high-risk newborns and eligible low-risk newborns diagnosed as having CDH in the first 3 months of life were kept to evaluate CDH incidence in the entire population. Low-risk newborns with CDH were identified by using our pediatrician referral base and at orthopedic hip clinic presentation.

Data were entered and analyzed using descriptive and comparative (χ^2) statistics performed with a computer program (SPSS-PC Plus, Microsoft, SPSS, Inc, Chicago, Ill [1986]).



Flow chart of screening and ultrasound (US) results. The cases of congenital dysplasia of the hip (CDH) are underscored. Asterisk indicates 1474 (83.3%) of 1772 screened for family history (26 [1.8%] positive); dagger, 12 of these infants had nonprotocol US studies for hip "clicks" (all were normal); and double dagger, initial US after 2 *weeks of harness treatment (immature).*

RESULTS

The Figure outlines the general schemata of the study that is described in detail below.

Screening

In the study period, 1772 of 1943 liveborn infants were eligible for study. In the eligible population, 883 (49.8%) were female, 1172 (66.6%) were white, and 365 (20.6%) were black. "Other" comprised 12.8%, who were predominantly Asian or Hispanic. Ninety-seven (5.5%) were high risk for CDH with at least one of the following: breech presentation, 73 babies (42 frank, nine complete, 22 footling); family history, 26 babies (12 primary—parent or sibling; 14 secondary—aunt/uncle or cousin); postural abnormalities, five babies (three metatarsus varus, one torticollis, one talipes equinovarus); and oligohydramnios, four babies. Eleven newborns had two risk factors.

In the eligible population, 4.5% were breech presentations, somewhat higher than the 3.5% expected incidence.[29] Family history questionnaire responses numbered 1474, or 83% of the 1772 eligible. The prevalence of a positive family history was 1.8%. A primary family history was seen in 0.8%.

The average birth weight (±0.6 kg) of the high-risk neonates was 3.3 kg. Seventy-one were delivered by cesarean section (73.2%) and 52 were first-born (53.6%). Seventy-nine were white (81.4%), eight (8.2%) were black, and 10 were other (10.3%). Whites composed a larger percentage of the high-risk group than the eligible group owing to their predominance in the family history category, consistent with their known higher prevalence.[30]

Of the 97 high-risk newborns, 69 (71.1%) participated in the US phase of the study: breech presentation, 52; family history, 19 (11 primary); postural abnormality, four; and oligohydramnios, four. Ten babies had two risk factors. Comparison of all eligible high-risk newborns with high-risk US participants revealed no significant differences by race, sex, rate of firstborns or cesarean section, or birth weight. Significantly, all 13 female babies with a family history of CDH (primary or secondary) participated in the US studies, including two who ultimately had CDH.

Five infants (four in the low-risk group and one in the high-risk group) were found to have unstable hips at the newborn examination (n=4) or 2-month examination (n=1) by their pediatrician and were successfully treated with a harness. An additional 12 infants from the low-risk group were referred for US examination of the hip for hip "clicks" independent of the study, and all were normal.

US Examination of High-Risk Infants

There were 69 infants who had 76 US examinations, including seven follow-up studies. The age at initial US was 48±24 days (range, 5 to 92 days). Four high-risk newborns had CDH, three of whom were given the diagnosis of CDH after normal findings from pediatric physical examinations. The fourth baby with CDH had unstable hips on newborn clinical examination and US did not affect her diagnosis. She was a frank breech presentation (buttocks presentation with legs extended) and was treated with a harness for 2 weeks before her initial US. Patient reports of the three high-risk infants whose conditions were diagnosed initially by US alone follow.

PATIENT REPORTS

PATIENT 1.—A 3.4-kg white baby girl, vertex presentation, was delivered vaginally; her mother was treated for CDH during infancy. Results of birth and 2-month pediatric physical examinations were normal. Ultrasound at 79 days showed bilateral immature hips with normal findings from the pediatric hip examination. Follow-up US at 100 days revealed bilateral deterioration to severe dysplasia with normal findings from pediatric and orthopedic physical examinations. Hip roentgenograms revealed bilateral dysplasia. She was successfully treated with a harness over 6 weeks until findings from US examination of her hip were normal. She had a normal gait and normal results of examination at 2½ years of age.

PATIENT 2.—A 3.0-kg white baby girl, vertex presentation, was delivered by cesarean section. Her brother and female first cousin were treated for CDH. Initial US at 75 days revealed severe left hip dysplasia with an immature right hip. Results of pediatric hip examinations at birth, 2 months, and 75 days were normal. Orthopedic examination at referral revealed decreased abduction of the left hip not appreciated by the pediatrician, although no hip instability was elicited. Hip roentgenograms revealed acetabular dysplasia. She was treated successfully with a harness over 13 weeks until results of her clinical and US examinations of the hip normalized. She has no residual effects at 2½ years of age.

PATIENT 3.—A 4.2-kg Hispanic baby girl, frank breech presentation, was delivered by cesarean section; there was no family history of CDH. Results of the hip examination at birth were normal. Ultrasound at 14 days showed mild dysplasia on the right and an immature left hip. Results of pediatric and orthopedic hip examinations were normal. The orthopedic surgeons elected to treat her with a harness over 8 weeks until the findings on US examination of her hip were normal. She has a normal gait and normal results of examination at 2½ years of age.

In all, eight (0.5%) of 1772 eligible infants were diagnosed as having CDH. The incidence of known CDH in the high-risk group was four (4.1%) of 97, significantly greater than in the low-risk group, four (0.2%) of 1675 ($P<.0001$). To our knowledge, no late cases of CDH have emerged, although patients may have been referred to other institutions for treatment. Thus, the true incidence of CDH in the low-risk group may be higher. The 28 high-risk infants who were not studied by US show no signs of late hip dysplasia clinically by pediatrician report.

COMMENT

Identification of newborns at high-risk for CDH using careful history and physical examination with subsequent US examination of these infants increases early detection of CDH. We detected four infants with hip dysplasia from 97 infants in the high-risk group using our screening protocol. The high incidence of dysplasia in the high-risk group is not surprising. What is surprising is the lack of, or subtlety of, the physical findings in these infants, even well after the neonatal period.

Only one of the four high-risk newborns with CDH had abnormal physical findings of the hip on their pediatrician's examination. Patient 1 was remarkable for the rapid deterioration of both her hips on follow-up US studies, while the findings from the clinical hip examination by her pediatrician and orthopedic surgeon remained normal. Although patient 2 had decreased hip abduction elicited by an orthopedic surgeon, she would have been "missed" based on the pediatrician's examination if she had not been identified as high risk and screened. The orthopedic surgeon also had the advantage of prior knowledge of the abnormal finding from the US examination of the hip.

Reports of clinically silent hip dysplasia are not new. In a study by Clark et al,[31] a similar high-risk group was screened by US in the first weeks of life. Eight (5.5%) of 158 high-risk infants (by our criteria) had CDH. This number is similar to our rate of 4.1%. Furthermore, five of eight patients of Clark et al had clinically silent CDH by physical examination. In these five clinically silent cases, two babies were a breech delivery and three had a family history of CDH. Cases such as these and ours may represent a type of CDH that is more associated with genetic factors and less apparent in the first months of life, but these patients may appear at a later age with a fully dislocated hip. Documentation of such cases has significant implication for the liability of pediatricians accused of missing CDH by physical examination.

Some radiologic CDH screening strategies have centered on nonselective mass screening using roentgenograms.[32] Because the infant hip is predominantly cartilage, conventional roentgenograms of hips in patients younger than 3 months of age are of limited usefulness for evaluation of hip dysplasia.[5,33] These roentgenographic approaches are not readily acceptable since roentgenographic screening exposes many infants to needless radiation, is not accurate in the assessment of CDH, and is costly.

Ultrasound evaluation of infants for CDH has become common practice at many pediatric centers. Its use for screening purposes remains controversial. In two separate German studies of more than 1000 newborns each, Szoke et al[20] and Langer[21] examined consecutive newborns with US in the first week of life. The incidence of borderline or immature hips ranged from 23% to more than 50% and

CDH treatment rates were high at 1% to 2%. Thus, the costs of mass screening in manpower, equipment, and time is high, as is the potential for false-positive examination results. Furthermore, the high treatment rates are alarming as harness treatment has a small risk of avascular necrosis. We believe our approach of selective screening later in infancy has the highest yield at the lowest cost.

The timing of the US examination is important when it is used for screening. The incidence of physiologically immature hips by US examination in the newborn period is nearly 50%, most requiring a follow-up study. While most of these neonates do not have CDH, the potential for overtreatment is real and the reinforcement of parental anxiety about CDH caused by follow-up studies would ultimately decrease participation in US screening. Therefore, in the absence of abnormal physical hip findings, we prefer to wait until 4 to 12 weeks of age to perform an US screening examination of the hip. This would reduce potentially unnecessary treatment in neonates while still identifying dysplasia early enough for successful harness treatment in young infants.[34] By striving to delay the US until after the neonatal period (mean, 48 days), the number of infants with a physiologically immature or borderline hip requiring US follow-up in this study was only 10%. At the same time, we have never cleared a hip as normal that subsequently was found to be dysplastic. One drawback of delaying the US past the newborn hospital period is decreased compliance, as 28 (29%) of our target infants would not return for the US examination. Adding the dynamic/stress maneuver[35,36] to the Graf method should further refine the definition of the physiologically immature and borderline type hips that require follow-up examinations, leading to even fewer follow-up studies. Although debate exists between the relative merits of the Graf method and the dynamic/stress techniques, we now believe that they are best used together as complementary studies in the diagnosis and treatment of CDH.

In one infant (patient 3), the US diagnosis of CDH was made early (14 days) with a mild degree of dysplasia. This child was treated promptly with a harness. It is possible that this mildly dysplastic hip could have improved spontaneously in this neonate. This situation would be avoided by strictly following screening timing guidelines.

In any screening program, cost is an important consideration. Ultrasound examination of the hip costs the same as roentgenographic examination of the hip ($85, October 1990) at our institution. If all 97 high-risk infants had been screened by US and no further CDH detected, the cost would be $9095 for 97 initial studies and 10 follow-up examinations. Harness treatment costs approximately $900 per infant. Thus, the cost of treating the three infants with silent CDH would be $2700. The total screening and treatment costs would be $11 795 or $3932 per infant with CDH. The cost of inpatient closed or open reduction of late-diagnosed CDH, plus related clinical services, ranges from $10 000 to more than $20 000 per case (Len Dias, MD, oral communication, October 1989). These direct costs of missed or delayed diagnosis do not include more difficult to measure "costs": pain, anxiety, time of both parent and child, and surgical/anesthetic risks. It is also difficult to assign a cost to a less than optimal outcome. Therefore, when weighed against the direct and indirect costs of hospitalization and potential residual disability, screening high-risk infants is both effective and economical.

Demographic considerations are important in any large-scale screening program. Female subjects are known to have at least a fourfold to 10-fold higher rate of CDH than male subjects.[4,5,24,33] All eight cases of CDH in this series were female. Costs could be halved if only female subjects were screened.

High-risk criteria could also be narrowed. Frank breech presentation is seen more commonly with CDH than other breech forms. A positive primary family history is more important than an extended family history for CDH risk. The published risk of CDH is 6% if an older child has CDH, 12% with one affected parent, and 36% with an affected child and parent.[37] In this study, two (6.1%) of 33 infants who were frank breech presentations had CDH and two (16.7%) of 12 infants with a primary family history of CDH had CDH. Congenital dysplasia of the hip was not detected either in infants born by complete or footling breech deliveries or in infants with an extended family history of CDH alone. The inclusion of congenital postural abnormalities and oligohydramnios as risk factors also needs to be critically evaluated with larger numbers. Further refinement of both the eligible population (including the inclusion of premature and ill newborns) and high-risk criteria may improve the screening yield, while maintaining a satisfactory rate of detection.

The obvious disadvantage of selective screening for CDH is the failure to detect CDH early in infants without CDH risk factors. In time, as US examination of the hip becomes standard for CDH diagnosis and management, as well as less costly, routine US screening of all infants in the second or third month of life may all but eliminate late missed CDH.

Since concluding our study, we have continued to recommend screening high-risk infants and have discovered numerous others with silent dysplasia. The high-risk US screening strategy has been well-accepted by parents, pediatricians, and orthopedic surgeons.

Our protocol meets accepted criteria for "screening tests"[38]: (1) CDH is a potentially serious condition and when diagnosed early, treatment is simple and effective; (2) the combination of history, physical, and select US examinations is safe, accurate, and cost-effective; and (3) the incidence of CDH is significantly higher in the select target population, as we and others have shown.

CONCLUSION

A careful history and physical examination should remain the cornerstone of any CDH screening strategy. Specific emphasis should be placed on eliciting a family history of CDH. Some cases of CDH are clinically silent in infancy and may be detected only by US. Infants with CDH risk factors should be screened with the use of US examination of the hip in the second or third month of life by experienced ultrasonographers even if the hips are clinically normal. Continuing studies are needed to further refine the risk criteria and optimal timing of US screening.

Karen Stouffer, RN, and Rosanne Losasso of Prentice Women's Hospital assisted with patient screening; the technologists from the Division of Ultrasound, Suzanne Devine and Nancy Wind, helped coordinate the studies; and Bobbie Rowe and Jan Roberts prepared the manuscript.

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A Clinical Trial of Fiberoptic Phototherapy vs Conventional Phototherapy

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• We conducted a randomized, controlled trial to compare fiberoptic phototherapy with conventional phototherapy in healthy jaundiced newborns with birth weights greater than 2500 g. Twelve patients received fiberoptic phototherapy and 14 patients received conventional phototherapy. There were no significant differences between the groups with respect to birth weight, gestational age, feeding method, presence of hemolytic disease, hematocrit, reticulocyte count, or initial serum bilirubin level. Measured irradiance at 425 to 475 nm for conventional phototherapy was greater than that of fiberoptic phototherapy (9.2±0.9 μW/cm^2 per nanometer vs 8.2±1.2 μW/cm^2 per nanometer). Both types of phototherapy lowered the level of serum bilirubin after 18 hours of therapy (fiberoptic group, from 231±29 to 210±24 μmol/L; conventional group, from 231±21 to 188±26 μmol/L), but the mean serum bilirubin level was lower after 18 hours of therapy in the conventional phototherapy group (188±26 vs 210±24 μmol/L). There were no side effects in either group of newborns. Both methods of phototherapy decreased the serum bilirubin level, but conventional phototherapy did so more effectively, probably because of its greater irradiance.

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Conventional phototherapy has a number of disadvantages: the newborn's eyes must be covered,[1] and the newborn is usually confined to an incubator. Both maneuvers may inhibit parent-child bonding,[2] and eye patching has caused airway obstruction.[3] In addition, conventional phototherapy is delivered as a horizontal band of light energy, incident on the newborn's torso and limbs. As such, the irradiant energy is maximal at the body surface nearest to the light source, but decreases significantly when measured at the lateral surfaces of the body.

A recently developed technique of phototherapy uses light from a fiberoptic source that is fanned out on a cummerbund. The cummerbund is wrapped around the newborn's torso. Eye patching and the use of an incubator are apparently unnecessary, and the light transmitted is nearly always perpendicular to the newborn's skin. Two recent studies suggest that this technique of phototherapy is probably as effective as conventional phototherapy.[4,5] We compared these two methods with regard to efficacy, side effects, and convenience.

PATIENTS AND METHODS

This study was approved by the Human Investigation Committee of the William Beaumont Hospital, Royal Oak, Mich, and consent for inclusion was obtained from one or both parents before randomization into the study or control group. Patients were enrolled from June 1989 through July 1990.

Criteria for inclusion in the study were the following: (1) healthy newborn with birth weight greater than 2500 g, (2) age greater than 24 hours, (3) no Rh blood group incompatibility, and (4) phototherapy ordered by the child's physician.

After a pilot study of five patients to familiarize the nursing staff with the fiberoptic phototherapy system, the newborns were randomly assigned (using a computer-generated random table) to receive either conventional phototherapy or fiberoptic phototherapy. The newborns were stratified by feeding method (breast or bottle) and ABO blood group incompatibility.

Conventional phototherapy was administered according to our usual nursery protocol using standard equipment. The phototherapy system consisted of four white (Sylvania Daylight, 20 W, F20T12/D, Sylvania GTE Products Corp, Hillsboro, NH) and four blue (General Electric, 20 W, F20T12-B, General Electric, Cleveland, Ohio) lamps (Olympic Bili-lite, Olympic Medical Corp, Seattle, Wash), placed 35 cm above the newborn, who was placed naked, except for diaper and eye patches, in an incubator and removed only for feedings. We measured irradiance at the newborn's head, chest, and abdomen (Olympic Bilimeter, Mark II, Olympic Medical Corp) and expressed the result as the mean of the measurements. The coefficient of variation of the bilimeter measurements (for 20 measurements at the same location under one light source) is 0.0003%.

In the fiberoptic phototherapy group (Wallaby Phototherapy System, Fiberoptic Medical Products Inc, Allentown, Pa), the cummerbund was wrapped snugly around the newborn's torso. The first 10 newborns in the fiberoptic phototherapy group were cared for in incubators, and the remaining two in a crib. All newborns wore eye patches. (Although eye patching is probably unnecessary with fiberoptic phototherapy, some light escapes beneath the cummerbund. Pending additional clinical experience, we thought that eye patching was prudent.) Irradiance was measured on the surface of the fiberoptic cummerbund, and is expressed as a mean of several measurements taken at different areas over the surface of the cummerbund.

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The decision to initiate phototherapy was made by the child's pediatrician. Total serum bilirubin concentration was measured just before the initiation of phototherapy (baseline), 6 hours after beginning phototherapy, and then every 12 hours until phototherapy was discontinued. A direct serum bilirubin measurement, direct Coomb's test, maternal and newborn blood typing, reticulocyte count, and complete blood cell count with peripheral smear were performed at, or shortly after, entry into the study. Newborns were removed from the study if their serum bilirubin level rose by more than 9 μmol/L per hour after phototherapy was initiated.

The child's temperature, while in the incubator, was measured continuously with a skin probe and was taken axillary every 4 hours with a glass mercury thermometer. All study newborns were cared for in the nursery.

Serum bilirubin levels were measured with direct spectrophotometry (Bilirubinometer, Advanced Instruments, Needham Heights, Mass, or Paramax, Irvine, Calif). Results were analyzed using paired and unpaired *t* tests for continuous variables and Fisher's Exact Test for categorical variables. Data are reported as means and SDs.

To estimate the sample size, we used a software program (True Epistat, Epistat Services, Richardson, Tex) and chose an effect size of 34 μmol/L as a clinically important difference in serum bilirubin levels at the end of phototherapy between the fiberoptic and the conventional group. Using $\alpha = .05$ (5% chance of a type I error), $\beta = .1$ (10% chance of a type II error), and an estimated SD of 24 μmol/L for the level of serum bilirubin after 18 hours, the number of patients required in each group was 12.

We also measured the irradiance of a fiberoptic panel at various distances from the surface. Ten measurements, from various areas on the surface of the cummerbund, were taken 0, 1, 2, 3, and 4 cm from the surface.

Table 1.—Clinical and Laboratory Characteristics of Study Groups*

Characteristic	Conventional Phototherapy (n=14)	Fiberoptic Phototherapy (n=12)	*P*
Gestational age, wk	37.6±2.9	38.7±1.9	.31
Birth weight, g	3255±525	3520±547	.22
Sex, M:F	8:6	9:3	.30
Race, white:other	13:1	11:1	.70
Feeding, breast:bottle	10:4	9:3	.60
Age phototherapy initiated, h	62.5±21	66.5±18	.61
ABO incompatibility:no incompatibility	5:9	5:7	.56
Positive Coombs':negative Coombs'	2:12	3:8	.37
Irradiance, μW/cm^2 per nanometer	9.2±0.9	8.2±1.2	.039
Hematocrit concentration	0.55±0.7	0.57±0.6	.37
Reticulocyte count, 10^9/L	421±543	349±533	.75
Apgar score at 1 min	7.2±2.0	7.5±1.4	.69
Apgar score at 5 min	8.6±0.8	8.7±0.6	.55
Mean axillary temperature during phototherapy, °C	37.1±0.2	37.1±0.2	.69

*Continuous data are reported as means±SDs.

RESULTS

There were no significant differences in clinical and laboratory characteristics between the two groups at entry into the study (Table 1). The measured irradiance, however, was significantly greater in the conventional phototherapy group (9.2±0.9 μW/cm^2 per nanometer vs 8.2±1.2 μW/cm^2 per nanometer, $P = .039$). The mean serum bilirubin levels during and after phototherapy are shown in Table 2. After 18 hours of phototherapy, the serum bilirubin level decreased significantly in both groups ($P = .008$ for the fiberoptic group, and $P = .00001$ for the conventional group), but was significantly lower in the conventional phototherapy group than in the fiberoptic phototherapy group. The mean decrement per hour in total serum bilirubin level for the first 18 hours of treatment was greater in the conventional phototherapy group than in the fiberoptic phototherapy group. The differences in serum bilirubin levels between the two groups remained statistically significant at 30 hours but not at 42 hours. However, only 11 (42%) of 26 newborns required phototherapy at 42 hours.

Two newborns, one from each group, were removed from the study before a 6-hour serum bilirubin level was measured. On receiving the baseline serum bilirubin levels (344 and 284 μmol/L, reported after phototherapy was initiated), their physicians chose to treat these newborns with two banks of conventional phototherapy. At 18 hours of treatment, two newborns in the fiberoptic group were changed to conventional phototherapy; one at the parents' request and one because the light bulb failed in the fiberoptic phototherapy system. Serum bilirubin levels in these newborns are included only to 18 hours.

The Figure shows the measured irradiance as a function of distance from the fiberoptic panel. Even a distance of 1 cm from the surface of the panel significantly reduced the irradiance.

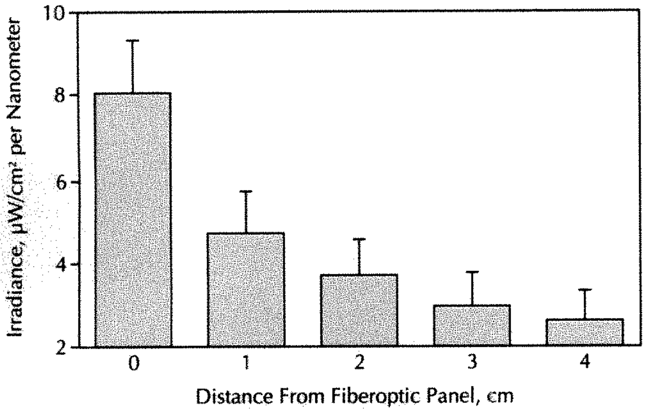
The cummerbund produced no abrasions and there were no rashes, temperature abnormalities, or other side effects in either group of newborns. Initially, the nurses preferred to administer conventional phototherapy.

Table 2.—Serum Bilirubin Levels During Phototherapy Treatment*

	Total Serum Bilirubin, μmol/L					Mean Decrement per Hour During First 18° h†
	Baseline	6 h	18 h	30 h	42 h	
Fiberoptic therapy	231±29 (n=12)	233±32 (n=12)	210±24 (n=12)	226±10 (n=4)	203±14 (n=4)	0.44±0.48
Conventional phototherapy	231±21 (n=14)	215±24 (n=14)	188±26 (n=13)	200±17 (n=8)	186±29 (n=7)	1.0±0.48
P (fiberoptic vs conventional)	.94	.14	.035	.025	.33	.0077

*Data are reported as means±SDs.

†Indicates mean decrement per hour of total serum bilirubin (as a percentage of initial total serum bilirubin level) during the first 18 hours of phototherapy.



Effect of distance from the fiberoptic panel on irradiance with fiberoptic phototherapy. Bars represent the means and SDs of 10 measurements.

There was some difficulty in maintaining a snug fit of the fiberoptic cummerbund against the skin. Subsequently, fiberoptic phototherapy gained some acceptance, especially when it was administered with the newborn in a crib. Several parents expressed satisfaction at being able to hold their child during phototherapy.

COMMENT

Both types of phototherapy decreased the serum bilirubin level, but conventional phototherapy did so more effectively than fiberoptic phototherapy, most likely because of the greater irradiance delivered. The irradiance of conventional phototherapy as measured at the newborn's skin was already greater than that of fiberoptic phototherapy when measured at the surface of the panel. This difference would probably be even greater if the irradiance of fiberoptic phototherapy could be measured at the newborn's skin. It was unfortunate, although not planned, that we actually compared two different dosages of phototherapy. Our intent was to compare the fiberoptic phototherapy system with conventional phototherapy as we currently use it. It is possible that increasing the irradiance of fiberoptic phototherapy would make it as effective as our conventional phototherapy.

In a nonrandomized trial of newborns with nonhemolytic jaundice, Rosenfeld et al[4] found that the serum bilirubin level was significantly lower after 48 hours of fiberoptic phototherapy than with conventional phototherapy, although the serum bilirubin levels after 12, 24, 36, and 60 hours of phototherapy were similar between the two groups. The irradiance of our conventional phototherapy units (9.2 μW/cm² per nanometer) was probably greater than that in their study, which "exceeded 7 μW/cm²/nm".

Gale et al[5] found no difference between conventional and fiberoptic phototherapy. In their study, the cummerbund was not wrapped around the newborns; they simply laid on the fiberoptic pad.

In our study and others, the newborns had mild elevations of their serum bilirubin levels. The decision to use phototherapy was made by the child's pediatrician, although the need for phototherapy in most of these newborns is questionable,[6,7] and its use may have adverse effects on maternal behavior and attitudes in the first few months of life.[8]

Fiberoptic phototherapy has some advantages over conventional phototherapy. Mothers can hold their newborns, and eye patching is probably unnecessary. However, in our sample, conventional phototherapy lowered the serum bilirubin level more effectively than fiberoptic phototherapy, probably because of its greater irradiance. Fiberoptic phototherapy has not been studied in newborns with severe hyperbilirubinemia (serum bilirubin level greater than 342 μmol/L). Although there is no reason to anticipate that it would not be effective at these levels, such studies should be done.

The fiberoptic phototherapy systems were supplied by Fiberoptic Medical Products Inc, Allentown, Pa.

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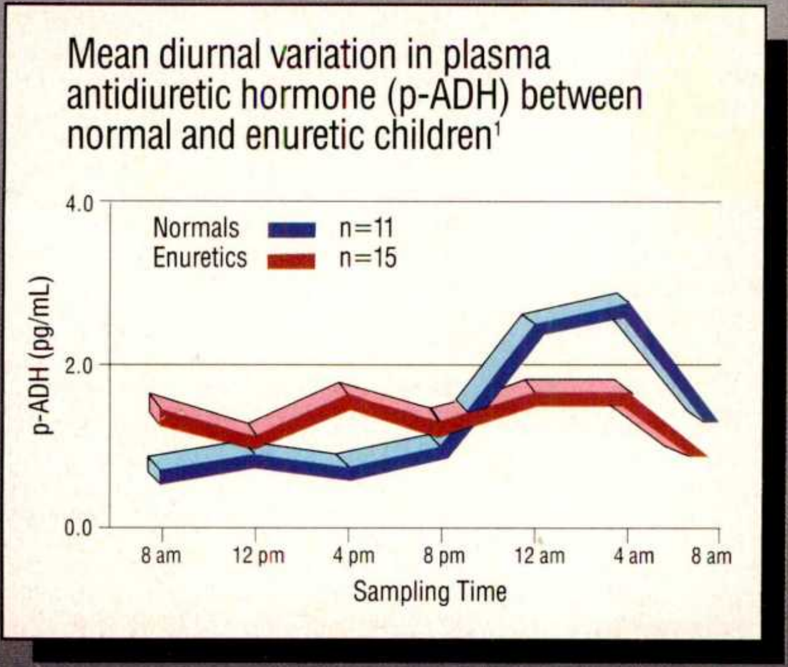
In Other AMA Journals

ARCHIVES OF NEUROLOGY

Headaches in Children Younger Than 7 Years of Age

Mary Lynn Chu, MD, Shlomo Shinnar, MD, PhD
(*Arch Neurol.* 1992;49:79-80)

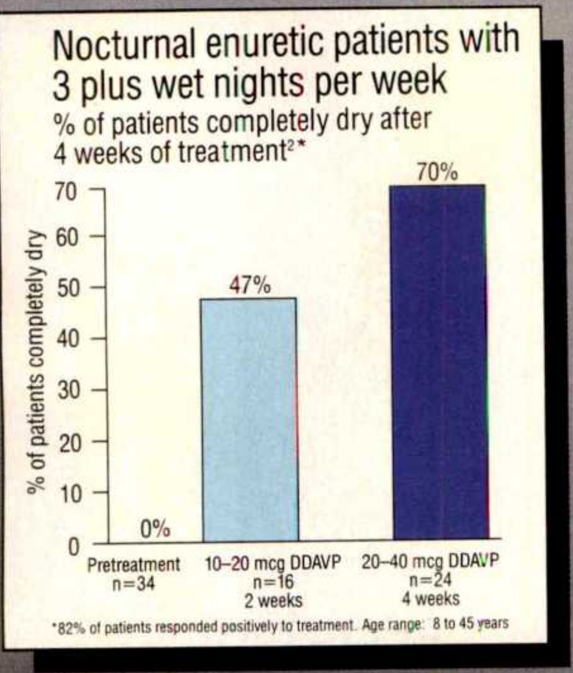
Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children[1]



Mean diurnal variation in plasma antidiuretic hormone (p-ADH) between normal and enuretic children[1]

The ADH Deficit

The first *physiologic* treatment for nocturnal enuresis

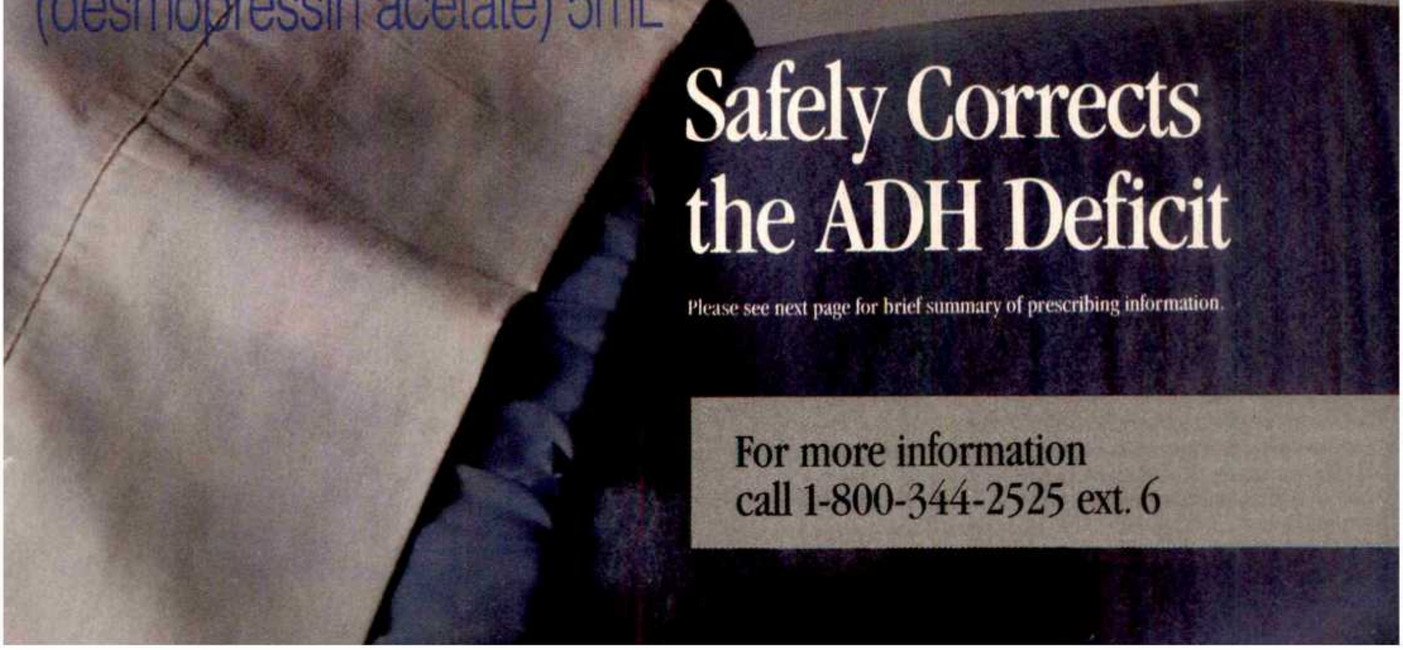


*82% of patients responded positively to treatment. Age range: 8 to 45 years

- DDAVP Nasal Spray, a synthetic analog of naturally occurring ADH, provides physiologic control of nighttime urine production in children 6 years of age or older[1-4]
- Clinically proven in all degrees of primary nocturnal enuresis, even in many patients resistant to imipramine and alarms[3]
- Easy to use — metered-dose nasal spray administered at bedtime
- Outstanding safety record in pediatric and adult patients[5]

DDAVP® Nasal Spray

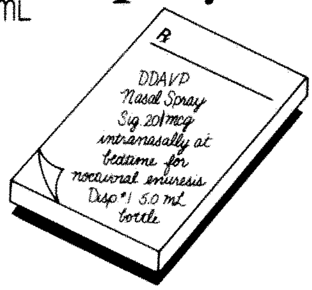
(desmopressin acetate) 5mL



Safely Corrects the ADH Deficit

Please see next page for brief summary of prescribing information.

For more information
call 1-800-344-2525 ext. 6



Nasal Spray

(desmopressin acetate) 5mL

Safely Corrects the ADH Deficit

CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:

General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	**PLACEBO (N=59)**	**DDAVP 20 mcg (N=60)**	**DDAVP 40 mcg (N=61)**
	%	%	%
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information. Rev. 6/89

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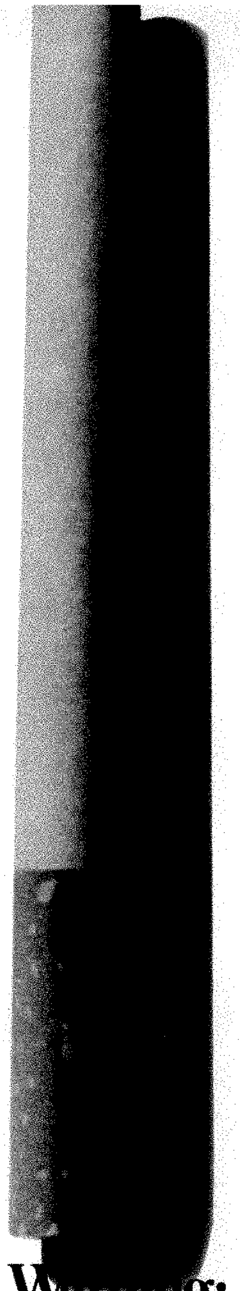

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Children's Advil®
(ibuprofen)
Suspension
100 mg/5mL

- Children's Advil® Suspension (10 mg/kg) provides better fever management than Tylenol®* (10 mg/kg) in fevers above 102.5°F†[1]
- Well-tolerated in short- and long-term use[1-3]
- Prolonged duration of action...up to eight hours of relief
- Pleasant fruit flavor enhances compliance

*Tylenol® (acetaminophen) is a registered trademark of McNeil Consumer Products Company.

†Labeled fever-reducing dose of acetaminophen drops and liquid is approximately 10-15 mg/kg.

Please see following page for brief summary of prescribing information.

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BY PRESCRIPTION ONLY

Children's
Advil®
(ibuprofen)
Suspension
100mg/5mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risks of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension. Ibuprofen can inhibit platelet aggregation and prolong bleeding time.

CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions. Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: in vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 6 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis, fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coomb's positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (eg., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children), 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

References:

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A Faculty–House Staff Retreat

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• There has been much discussion regarding the causes of stress in residency training programs and solutions to alleviate the pressure. As a partial solution, we have found discussions of retreats for pediatric interns in the medical literature, but no discussion of departmentwide retreats. Since the early 1970s, the University of Wisconsin (Madison) Department of Pediatrics has held a faculty–house staff retreat every 2 years. The more recent retreats used process-oriented discussions in its goals of fostering understanding through group communication to reduce stress. The 1989 agenda was an expansion of previous efforts with extensive faculty and house staff involvement before, during, and after the retreat. The purposes of this article are to review the literature on the use of retreats in various settings, especially residency training programs; describe the past and present use of retreats by the University of Wisconsin Department of Pediatrics; describe the 1989 retreat; and describe the positive and negative aspects relating to retreats as we have used them. We believe our retreat is unique, serves many purposes, and has been a successful tool for relieving residency stress.

(*AJDC.* 1992;146:243-248)

Stress is inevitable in the lives of physicians. This is especially true for new physicians during their period of residency training. Lazarus et al[1] defined stress as "any event in which environmental or internal demands (or both) tax or exceed the adaptive resources of an individual, social system, or tissue system." Perceptions of stress, coping strategies, and the ability to manage stress vary among individuals, especially those in training situations. Although persistent stress may be detrimental during training, limited amounts may be necessary for residents to learn management of stress accompanying their medical careers. Causes of stress and solutions to reduce stress during residency training are popular subjects.[2-12] Conferences addressing house staff stress have been organized.[13-15] Professional governing bodies and organizations,[16-17] state legislatures, and judicial bodies[18-23] have recommended limitation of work hours to minimize stress. Many programs and institutions attempt to relieve stress and its symptoms by providing social and psychological support.[24-27] One traditional method is the retreat[27-30], defined by Webster's[31] as "a period of group withdrawal for prayer, meditation, study, and instruction under a director."

In practice, retreats in both private industry and medicine use psychotherapy groups, encounter groups, training groups, and process-oriented discussion groups, or combinations of these forms, to meet their goals. Process-oriented groups may be most effective in support of trainees with developmental stresses and are commonly used for stress reduction. They use group processes to enable members to take a major responsibility for the group's direction, and engender trust in the group so that members are free to spontaneously express their beliefs about the issues under discussion. The group fosters a sense of "permission" to voice opinions, and enables participants the gratification of knowing that others share similar beliefs.[27]

Private industries have long recognized the value of retreats not only for stress reduction, but also to promote job satisfaction and ultimately improve productivity.[28] One of the first reported corporate retreats was held by the National Cash Register Corporation in 1894, with other major corporations, including 3M, Conoco, Goodyear, and Alcoa, reporting that they also conduct regular retreats (*Industry Week.* July 10, 1978:61). Originally, corporate retreats were for executives, but increasingly are used to hold workshops, training programs, and strategy sessions for other employees (*Industry Week.* July 10, 1978:61). Industrial retreats have been reported of variable duration, from simple and modest to elaborate and expensive settings (*Canadian Business.* August 1987:21). Federal Express

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Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

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held a retreat in the wilderness to develop teamwork and leadership skills among its employees (*Personnel.* July 1986:4). Outside facilitators may be used to contribute objectivity, maintain focus, and introduce new techniques for problem solving and consensus development.

In the medical literature, retreats typically have been used either for medical students, residents, or faculty. One pharmacy residency program, however, brought residents and preceptors together to review and modify its program.[32] Bergman et al[33] and Rothenberg and Rothenberg[34] at the University of Washington (Seattle) described a 5-day retreat for pediatric interns early in their first year. Its purpose was twofold: (1) to improve interest in primary care pediatrics, and (2) to provide an atmosphere in which interns would interact and form a social network. Doughty[28] described a 2-day retreat for first-year residents late in the first year. The first day was devoted to reviewing the year, sharing experiences, and discussing conflicts and difficult situations in a group format. On the second day, the meeting was run by professional facilitators who expanded on the issues raised the previous day. Other departments commonly hold social gatherings for faculty and house staff, seminars for house staff on topics of clinical importance, such as death and dying, as well as general discussions about residency training.[35,36]

We report here a model for a department-wide retreat, including the entire faculty and house staff in a process-oriented group format. During these retreats, a wide range of issues and purposes, including physician stress and the content and structure of the residency training program, were addressed. We could find no other examples in the literature of a broadly based retreat, addressing a broad range of issues, and resulting in major substantive programmatic changes.

UNIVERSITY OF WISCONSIN PEDIATRIC RETREATS

The University of Wisconsin Department of Pediatrics has 34 residents and approximately 50 full-time faculty members. Retreats began in the early 1970s and have evolved over time. Originally including pediatric faculty, the chief resident, and selected practicing pediatricians from the community and state, the discussion centered on policy and program development, medical student education, and the role of private practitioners in student and resident education. By the late 1970s, the retreats had become a biannual event, included all faculty and house staff, and were held at a hotel conference center 50 miles from the hospital. The retreats concentrated primarily on residency training issues, including the content of the training program, definition of educational objectives, methods of house staff and faculty evaluation, and faculty–house staff interaction. Over time, the retreats evolved to provide an opportunity for ventilation of frustrations, an increase in exchange of ideas, recreation, meals, informal evening "rap" sessions, and social time. Some changes in program content and policy resulted from these retreats, but their primary value was ventilation of concerns and improved awareness of varying viewpoints. Comments made in follow-up surveys were consistently positive, with the exception of some comments concerning lack of direct policy changes.

Since 1982, these department-wide "maxi-retreats," still held biannually, have been interspersed with "mini-retreats," held once or twice a year for each group (residents in their first, second, and third year). The mini-retreats are held in the program director's home, and include the department chair, chief resident, and members of each year's group. They expand on specific topics that are discussed in the larger retreats and are of special interest to the smaller group, and complement the maxi-retreats. Occasionally, spouses and significant others attend to discuss tensions involving work and personal life, which would be difficult to do at the larger maxi-retreat.

THE 1989 MAXI-RETREAT

Preparation: Identification of the Issues

The retreat had the vigorous support and financial backing of the department chair, in consultation with the department faculty at monthly department meetings. The chief resident (P.J.K.), in collaboration with the program director (N.C.F.), was responsible for planning. The retreat was scheduled for a 22-hour period from 2 PM Friday, March 31, to noon Saturday, April 1, 1989. Three months before the event, a volunteer planning committee of residents prepared a preliminary list of problem areas in the training program and worked with the chief resident and program director. This committee revised previous faculty and house staff survey questionnaires, identified problems and proposed solutions, recruited volunteers, and formed four other committees. Each committee consisted of at least two residents and one faculty member and was given the following topics: (1) substantive changes in program content; (2) faculty–house staff interactions; (3) methods for unifying the residents; and (4) issues in the Division of General Pediatrics and Adolescent Medicine. Each committee had a faculty and resident co-chair, with the residents assuming most of the leadership responsibility, including scheduling, recording, and coordinating with other committees. The first committee meetings were scheduled 6 weeks before the retreat. Meetings lasted 1 or 2 hours, with variable meeting times and places, such as 6:45 AM in the cafeteria, brown bag lunches during workdays, 6:30 PM restaurant dinners, and 8:30 PM meetings in faculty homes. Attendance was consistently near 100%. Extensive minutes were taken at each meeting and widely distributed. Twenty-four-hour availability of a computer and printer for house staff was essential in preparing questionnaires and recording responses, recording minutes of the meetings, and preparing other materials for the actual retreat.

Development of Concrete Proposals

One month before the retreat, the committees formulated specific proposals to present at the retreat. Since many issues were interrelated, committee chairs informed each other and the chief resident of their progress to avoid overlap. Some committees recruited additional department members who showed interest, shared insight, or had relevant experiences. During this time, there were increased numbers of informal discussions in the hallways, wards, and clinics, and before and after conferences.

The penultimate week included a meeting of committee chairs to discuss and complete proposals, condensing weeks of work into multiple half-hour presentations and proposals. By this time, several projects were completed and printed for general distribution: (1) the retreat survey results, a 60-page document providing extensive quantitative and qualitative data on faculty and house staff views on a variety of program-related issues; (2) an annotated bibliography discussing the content of recent articles dealing with resident stress; (3) an "Intern Survival Manual," an attractive pamphlet describing services and recreational opportunities in the region, including child care, best restaurants, day trips, outdoor activities, cleaners, hair salons, car care, and so on.

The Actual Retreat

All residents were relieved of clinical duties from noon Friday through 2 PM Saturday, except for three senior residents who returned Saturday morning. Clinical care at the department's wards, clinics, and nurseries was provided by fellows, residents from other departments on pediatric rotations, full-time emergency room personnel, senior medical students serving as subinterns, 10 pediatric faculty members who did not attend the retreat, and four community pediatricians. Those providing clinical care duties for the pediatric residents were extremely supportive of the retreat, served without compensation, and were greatly appreciated. The appreciation was epitomized in a comment by a first-year pediatric resident: "Thanks for staying and fighting while we retreated."

The final retreat agenda (Table 1) identified three sessions: (1) Substantive Programmatic Changes; (2) Resident Stress and Unifying Residents Committee Proposals; and (3) Issues in General Pediatrics and Adolescent Medicine, particularly involving ambulatory primary care training. The program director chaired the meeting. Final attendance included 67 people: 35 of 70 invited faculty members and 32 of 34 house staff members. Most faculty who did not attend had previous commitments or covered for those who attended the retreat. Each person received a folder with extensive summaries of the committee reports and proposals, and completed projects, and were seated at a large table. Several opportunities for social interaction were structured into the retreat, including meals, recreation (eg, swimming, tennis, and hikes), and a late-night gathering.

At least two proposals for each major problem were identified (Table 2). Three examples of problems and solutions are discussed in detail below.

Stress.—Increasing acuteness of patient care, long hours, and sleep deprivation, especially during the university hospital rotations, were expressed. Many first-year pediatric residents assigned to wards were spending a great number of hours in these wards and were chronically fatigued and inefficient. They were scheduled on call every fourth night and often stayed at the hospital until after 8 PM every weekday, including the days after call. Suggested efforts to address this problem included assigning one intern to a "mole" or "nighthawk" rotation consisting of 8 PM to 8 AM on-call ward coverage Sunday through Thursday evenings. First-year pediatric residents who are assigned to ward rotations would be limited to "short call" until 10 or 11 PM every fourth night to assist the mole's transition and would stay on call in the hospital only Friday or Saturday nights when there was no mole.

Oncology Patients.—Volume and complexity displacing time and teaching for general pediatric patients, protocol management forcing residents into "physician assistant" roles, poor outcomes of patients, and deaths of patients, sometimes in groups, were identified. The proposed solution included removing "sick" oncology pa-

Table 1.—Retreat Agenda

	Friday, March 31
2:00 PM-2:10 PM	Introduction—Department Chair and Program Director
Substantive Programmatic Changes	
2:10 PM-2:30 PM	Introduction to Committee on Potential Program Changes
2:30 PM-3:00 PM	Presentation of Proposals for Change 1. Hematology/oncology rotations for residents 2. Subspecialty requirements for residents 3. Presence of postgraduate level 3 in pediatric intensive care unit 4. House staffing the new Intermediate Care Unit 5. Required postgraduate level 3 rotation at outside hospital 6. Enhancement of normal newborn resident rotation 7. Scheduling of house staff vacations
3:00 PM-3:15 PM	Break
3:15 PM-4:15 PM	Discussion of Above Proposals
4:15 PM-5:00 PM	Presentation/Discussion of Proposals for Call Schedule Changes 1. Resident backup systems for call 2. Resident nighthawk or mole rotation
5:00 PM-8:00 PM	Exercise and Dinner Break
8:00 PM-10:00 PM	Presentation/Discussion of Faculty-House Staff Interactions Committee Proposals 1. Greater resident autonomy and initiative: "The 8 Commandments of Communication" 2. Greater consistency: using objectives and rotation calendars for residents 3. Improvements in the evaluation process
10:00 PM-12:00 AM	Social Hour
	Saturday, April 1
7:00 AM-9:00 AM	Exercise and Breakfast
Resident Stress and Unifying Residents Committee Proposals	
9:00 AM-9:20 AM	Presentation/Discussion of Unifying Residents Report 1. Present activities 2. New activities 3. Designating "House Staff Counselor": used as educator in conferences and problem solver in acute settings
9:20 AM-10:00 AM	Discussion of Resident Stress: An Annotated Bibliography
Issues in General Pediatrics	
10:00 AM-11:00 AM	Presentation/Discussion of General Pediatrics and Adolescent Medicine Proposals 1. Improvement of morning conference 2. Emergency room, weekend, and call problems/discussion 3. Weekly continuity clinic: problems/discussion 4. Increased involvement of pediatric nurse practitioners in resident teaching
11:00 AM-11:30 AM	Loose Ends/Summary

Table 2.—Problems and Solutions

Problems	Solutions
Hematologic/oncologic patients in the general ward create stress for many residents	Reapportioning of resident coverage for inpatients
Lack of consistency in subspecialty rotations without clear objectives, calendars and time set aside for tutorials, and many faculty are reluctant to discuss resident evaluations with the resident	Requirement of educational objectives and schedule for all rotations with time set aside for evaluations
Unclear role of postgraduate level 3 rotation in pediatric intensive care unit	Definition of concrete goals
Formation of a new unit, the Intermediate Care Unit	Plan of resident coverage and attending backup
A required postgraduate level 3 community hospital rotation had not met its goals	Making this rotation elective pending approval through administrations
Normal nursery rotation was not fully developed	Assignment of one person as director of newborn nursery education
Scheduling of house staff vacations during electives interfered with teaching during the rotation	Stricter adherence to vacation at beginning or end of rotation and limiting vacation to a maximum number of days on certain elective rotations
Increasing use of the backup system in call schedule causing strain in the system	The discussion reaffirmed that present backup system is a good one
Lack of sleep for postgraduate level 1 residents on university hospital call has led to stress, interference with teaching	Creation of a nighthawk position and short call to allow postgraduate level 1 residents to be better rested on weekdays
Faculty–house staff interactions are too few and too stressed, commitment toward teaching varies, attending physicians rarely observe house staff in action	A prolonged discussion allowing the concerns to be voiced and suggestions for change, ie, "8 commandments of faculty–house staff communication"
Training is skewed toward tertiary care	Increased involvement and teaching with the general team attending with team patients and increased use of general team "consults" for teaching with other patients
Although house staff have shown camaraderie, there is still room for improvement	Residents beginning new projects, such as "Intern Survival Manual" and others to increase supportive networks
What is resident stress and is it worse than when attending physicians were residents?	Review and discussion of recent literature regarding causes, solutions for stress, and strategies for coping and adaptation
Evaluation forms out of date	Evaluation forms to be updated
The General Pediatrics division morning conference has great potential to be more educational	Suggestions for improving the teaching value of general pediatric conferences
Problems with emergency room, weekend coverage, and call may decrease the educational experience during General Pediatrics rotations	Work began on the development of a new Sunday urgent care clinic to improve patient care and resident education
Weekly continuity clinics creating stressful situations	Improvements in scheduling of continuity clinics
Pediatric nurse practitioners are a poorly utilized teaching resource	Suggestions for increased resident–pediatric nurse practitioner teaching sessions

tients from the general inpatient service and reassigning them to a single second-year pediatric resident who is responsible for covering a geographic oncology unit. This person would presumably be more efficient; would free-up the first-year pediatric residents in the wards so they would be able to spend more time with general patients; and would substitute one difficult month for the existing arrangement in which all ward patients, for first- and third-year residents, were dominated by oncology patients. One additional residency position was added to the program shortly before the retreat, allowing the first two solutions to be enacted without major changes in the existing resident schedule.

Subspecialty Rotations.—Some residents noted inconsistent and inadequate identification of educational objectives for each service, and variable and unstructured teaching, depending on attending physician. The recommendations included the appointment of a subspecialty committee made up of faculty and house staff to help ensure the development of objectives, core readings, a self-assessment examination, and a structured schedule for each rotation.

In all, 20 proposals for change were generated by the retreat. The atmosphere was congenial with spirited discussion by faculty and house staff. House staff did not appear or report being inhibited.

Follow-up After the Retreat

One week after the retreat, a brief summary with deadlines for action was distributed to all faculty and house staff. Committees in charge of follow-up assignments met, and informal discussions continued to pervade the daily life of the department for weeks afterward. Additional surveys were conducted by various committees.

Past residents were asked to evaluate the strengths and weaknesses of the program in meeting practice needs, and division directors were asked to submit a description of their resident rotations with core objectives. Two postretreat questionnaires were designed and distributed to all attendees 1 month after the retreat and 1 year later. Postretreat data, including answers to questions and written comments, were extremely favorable in both surveys. Many respondents made comments that reflected additional thoughts about the problems and solutions not brought up at the retreat. Others offered suggestions for future retreat topics. An overwhelming majority (approximately 90%) of those who responded at 1 year believed that the changes implemented after the retreat had improved the provision of patient care and/or quality of the residency training program.

The most dramatic concrete results were the establishment of the "nighthawk" rotation, elimination of the sleep-in requirements for university ward first-year residents, and the removal of oncology patients from the university general ward service. Six months into the next academic year it was clear, by observation and admission, that the ward interns were better rested and consistently positive about the internship, and that morale was at an all-time high. For those responding to the 1 year questionnaire, there was unanimous support of the "nighthawk" rotation.

OBSERVATIONS CONCERNING THE RETREATS

Negative Aspects

Although efforts were made to limit the negative aspects of the retreat, some problems developed. The final decision-making process was not defined before the retreat. The tradition of the department was consensus development. The final decisions regarding implementation were made by the program director and department chair. Newer faculty members and house staff would have benefited from clarification of this process before the actual retreat began. Despite extraordinary house staff involvement in the process and outcome, many believed they were left out. Most of the work preparing for and conducting the retreat was carried out by second- and third-year residents. Although first-year residents were represented on committees, many were not as heavily involved as the senior residents, perhaps due to heavier clinical time commitments. Changes therefore had been made by a departing group, with those persons most affected least involved in the process. To address this concern, we scheduled a mini-retreat with the group of first-year residents to openly discuss the proposed changes. In addition, during the planning phases, we were concerned that frustrations and negative attitudes might be aired without adequate resolution. Broad participation and concrete results limited the frustrations and produced broad, though not unanimous, acceptance.

Doughty[28] experienced other negative aspects of retreats that we did not experience. These included residents developing grandiose unfulfilled expectations of immediate improvement, aggravation of preexisting interpersonal conflicts, lack of honesty or involvement by participants, and deviation from the planned agenda during the retreat. We believe that our modification of process-oriented discussion, with extensive preparation, defined agenda, broad participation, and congenial atmosphere limited the potential for these outcomes.

Positive Aspects

There were two obvious general benefits. First, the retreat was clearly a major activity of the department for at least 2 months surrounding the actual meeting. This continuous "peri-retreat" activity, involving hundreds of person-hours and intensive discussion, was one of the major benefits of the retreat. The detailed preparation facilitated considerable understanding and awareness among house staff and faculty of each other's views and concerns. The involvement of many faculty and house staff members working together improved the morale and feeling of togetherness within the department. Many residents had been unaware of the depth of interest of many faculty in the residency program. Some faculty members had previously considered the residents too passive in their education and were impressed and encouraged at the energetic and assertive house staff involvement in creative reforms. Second, the department enhanced its monitoring of resident subspecialty rotations to ensure ongoing, high-quality educational experiences.

There were obvious procedural and substantive benefits. Three specific changes in the residency program were the direct result of suggestions made during the retreat. These included the relief of the stress on the ward interns through the "nighthawk" rotation, relief from responsibility for oncology patients that produced a new cohort of better rested and more enthusiastic first-year residents, and relief of a congested Sunday emergency room by establishment of a Sunday urgent care clinic to facilitate patient care and resident education. There were less dramatic but important benefits. Many aspects of the training program were carefully evaluated and identified as good, reaffirming many strengths of the department and enhancing pride in the training program. Many easily addressed concerns were reported to the group. Several committees completed projects that were noncontroversial and widely appreciated, including the "Intern Survival Manual" previously mentioned, and a directory of residents, including names and birth dates of spouses and children. Nearly completed projects in the General Pediatrics division were discussed with and approved by the group, facilitating their prompt implementation.

CONCLUSION

Although department-wide retreats are not in common use, this combined faculty and house staff retreat has been a useful tool. The effort, led primarily by energetic house staff members, with close involvement of department leadership and faculty, produced many substantial reforms in the residency training program. The retreat process enhanced faculty and house staff relationships, directly and indirectly tackled many stressful issues, and produced both immediate and long-term benefits for the program. From our experiences, we make the following recommendations for successful retreats: (1) preparation must be done before the retreat, (2) the retreat must have a focus, with minimal deviation from the agenda, (3) the discussions should be solution-oriented, (4) the process should involve interaction in an environment that encourages all participants to speak, and (5) adequate follow-up must be ensured.

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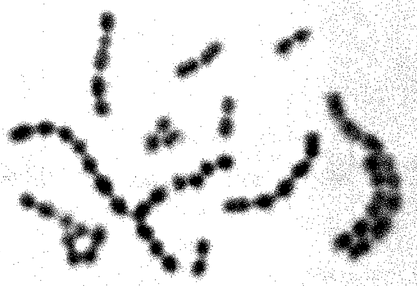

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	<0.3	0.3-0.7	>0.7
2 wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

* From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride supplementation: Revised dosage schedule. *Pediatrics* 1986; 77(5):758-761.

** The Committee recommends that all breast-fed infants be evaluated shortly after birth to determine their need for fluoride supplementation. In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula. No fluoride is present in the water used to produce Ready-To-Use formula.

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POLY-VI-FLOR 0.5 mg with Iron	Drops	50 mL Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 mL Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 mL Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 mL Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

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SPECIAL FEATURE

Radiological Case of the Month

Pat Oades, MBBS, MRCP, Roger Buchdal, MD, MRCP (Contributors);
Beverly P. Wood, MD (Section Editor)

A 5-year-old girl was found choking and breathless by her father. She slumped forward and experienced a short generalized convulsion. Her parents had noted noisy, irregular breathing at night beginning at age 18 months. This had been diagnosed by her general practitioner as mild asthma. On admission to the hospital, she was postictal and cyanotic, with costal retractions and crackles heard at both lung bases. A chest roentgenogram was obtained (Fig 1). A diagnosis of hypoxic convulsion associated with aspiration pneumonia was made. After 24 hours of assisted ventilation, she made a steady recovery, with resolution of the roentgenographic abnormalities.

One month later, a barium esophagogram was obtained to investigate the possible cause of aspiration (Fig 2). During the next 6 weeks, she complained of dizziness and became unsteady on her feet. Soon afterward, she again developed pneumonia and was admitted to the hospital. Results of neurologic examination revealed truncal ataxia; a weak, fasciculating tongue; and a poor gag reflex. Her respiratory rate was low, and she had apneic episodes. Continuous transcutaneous monitoring of P_{O_2} and P_{CO_2} levels confirmed periods of hypercapnia associated with hypoxia that are typical of central hypoventilation. A magnetic resonance scan of the brain was performed (Fig 3).

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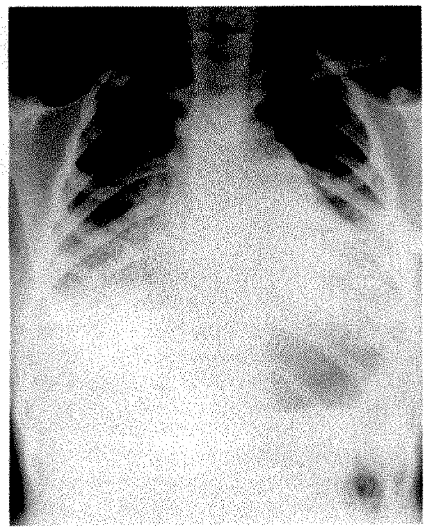

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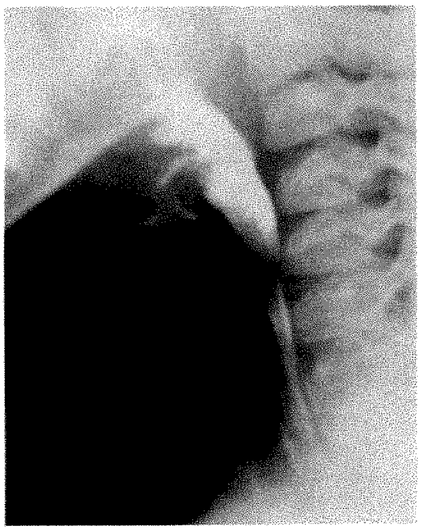

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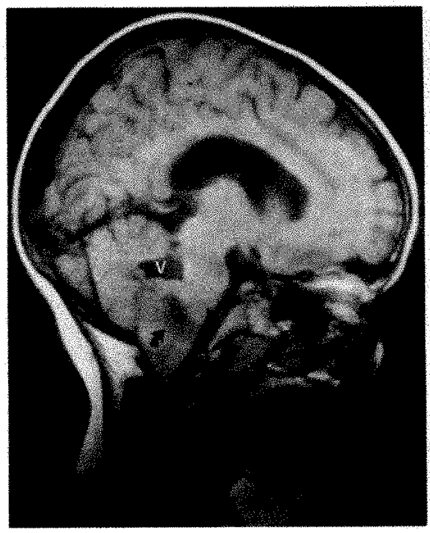

Figure 3.

Denouement and Discussion

Brain-Stem Astrocytoma Presenting With Aspiration Pneumonia

Fig 1.—*Chest roentgenogram shows bilateral basilar consolidation, indicating pneumonia.*

Fig 2.—*Barium esophagogram. Swallowing was initiated with normal peristalsis. No fistula was present. A trickle of barium passed from the hypopharynx to the upper airway.*

Fig 3.—*Results of a T_1-weighted magnetic resonance scan of the brain in the sagittal plane shows a tumor 4 cm in diameter (arrow) arising from the posterior aspect of the medulla oblongata and compressing it and the fourth ventricle (V). The inferior vermis, pons, and midbrain are all displaced upward. Dilation of the third and lateral ventricles results.*

Discovery of a brain-stem tumor with magnetic resonance imaging was followed by stereotactic biopsy of the lesion, which confirmed a grade 2 astrocytoma. The tumor was considered inoperable and she was referred for radiation therapy. She experienced respiratory arrest after her initial treatment with dexamethasone, with subsequent irreversible brain damage and death.

Tumors of the central nervous system are common solid tumors of childhood, accounting for more than 15% of malignant neoplasms identified in children.[1] More than half of these occur in the posterior fossa, and brain stem glioma accounts for 10% of all cases. The tumors are usually slow growing, causing symptoms because of compression and structural displacement rather than destruction. Prognosis depends on results of histologic examination and rate of growth and is worse for tumors below the midbrain.[2]

The common presenting features of a brain-stem glioma include ataxia, headache, motor loss, and cranial nerve palsies.[2] However, brain-stem gliomas developing with late-onset gastroesophageal reflux and disordered esophageal motility associated with damage to efferent fibers from the dorsal vagal nucleus and the nucleus ambiguus are also recognized.[3,4] In our patient, aspiration pneumonia occurred in relation to faulty airway protection during swallowing, as shown on the barium esophagogram. This presumably reflected damaged innervation of the pharyngeal muscles caused by pressure on the lower cranial nerve nuclei. It is conceivable that the noisy, irregular breathing at night that preceded the first admission to the hospital was related to damage in this region of the brain stem. The subsequent development of a wasted, fasciculating tongue and truncal ataxia is explained by encroachment of tumor on the 12th cranial nerve nuclei and the cerebellar vermis, respectively.

The patient's central hypoventilation may have been the result of compression of the respiratory center in the reticular formation of the brain stem. Central hypoventilation has been described in patients after surgery of the high cervical cord and brain stem.[5] Characteristics include an elevated P_{CO_2} level, hypoxia, and a flat CO_2/ventilation response curve in the absence of airway obstruction. Progressive, severe, and prolonged expiratory apnea, another disorder of respiratory control, has also been described in association with medullary brain-stem glioma[6] and other brain-stem abnormalities, such as myelomeningocele and the Arnold-Chiari malformation.[7]

Magnetic resonance imaging is the investigative tool of choice for confirming brain-stem lesions at an early stage, as computed tomography does not provide adequate delineation of brain-stem structures and may show normal results in patients who were subsequently found to have brain-stem glioma at postmortem examination.[3]

Brain-stem tumors may occur with headache and focal neurologic abnormalities or with swallowing disorders, including aspiration, and disorders of respiratory control, such as central hypoventilation and prolonged expiratory apnea.

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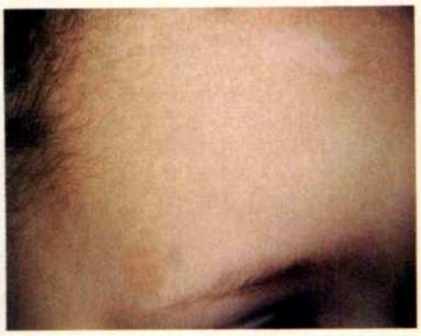
Picture of the Month

Walter W. Tunnessen, Jr, MD (Contributor and Section Editor)



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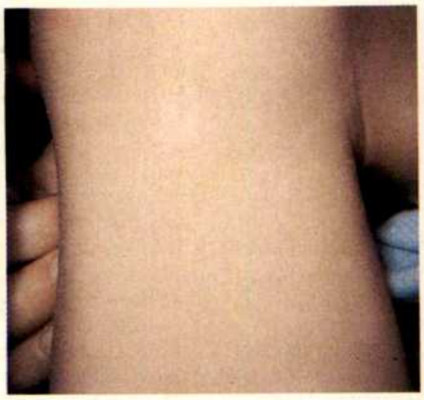

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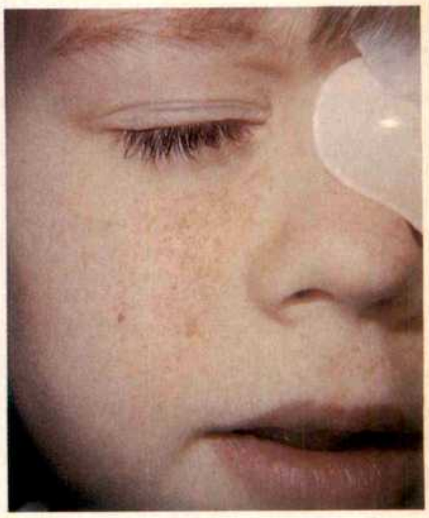

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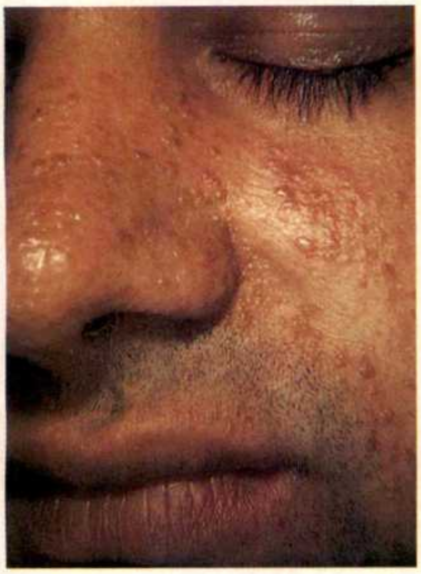

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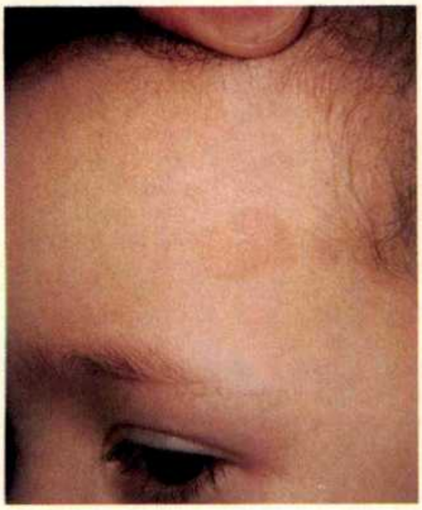

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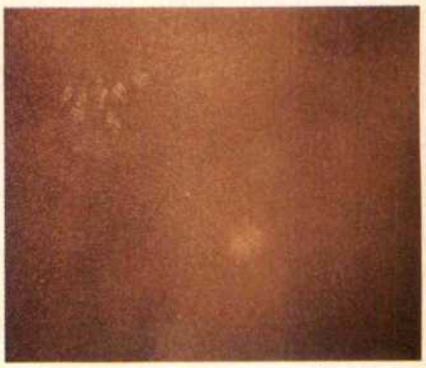

Figure 6.

The Editors welcome contributions to Picture of the Month *and* Radiological Case of the Month. *Those who wish to contribute should send their manuscripts to Dr Tunnessen* (Picture of the Month), *The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, or Dr Wood* (Radiological Case of the Month), *Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Accepted for publication April 15, 1991.

From The Children's Hospital of Philadelphia (Pa).

Reprint requests to The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Tunnessen).

Denouement and Discussion

Tuberous Sclerosis

Figs 1 and 2.—*Hypopigmented macules on the forehead and knee.*

Figs 3 and 4.—*Adenoma sebaceum in a 6-year-old patient and in an adult patient.*

Fig 5.—*A typical fibrous plaque on the forehead.*

Fig 6.—*A hypopigmented macule and shagreen patch on the abdomen of a 6-year-old patient with a learning disability.*

Manifestations

Tuberous sclerosis (TS) was first described by von Recklinghausen in 1862. In 1880, Bourneville used the term *tuberous* to describe the potatolike findings in the cerebral gyri of affected individuals and the triad of mental retardation, seizures, and adenoma sebaceum (angiofibromas) associated with this disease. This neurocutaneous disorder is much more common than previously thought, has wide variability in its presentation, and affects many body systems.

The criteria for diagnosis give some indication of the variability of this genetic disorder. Criteria for the definite diagnosis of TS include one or more of the following conditions:[1] facial angiofibroma; ungal fibroma; retinal hamartoma; cortical tuber; subependymal glial nodule; and renal angiomyolipoma. Criteria for a presumptive diagnosis of TS include two or more of the following conditions: hypomelanotic macule; multicystic kidney; shagreen patch; cardiac rhabdomyoma; gingival fibroma; pulmonary lymphangiomyomatosis; dental enamel pits; peripapillary retinal hamartoma; infantile spasms; a single renal angiomyolipoma; multicystic kidney; "honeycomb" lung on radiographic examination; myotonic, tonic, or atonic seizures; and an immediate relative with TS.

Cutaneous findings suggestive of TS are present in 90% to 95% of affected individuals. They may be subtle, and they demand careful inspection, particularly with the use of a Woods lamp, to detect the hypopigmented macules in fair-skinned individuals. It was thought that hypopigmented macules were present at birth, but prospective studies have shown that they may appear months to years later. Facial angiofibromas generally appear between the ages of 4 and 6 years. They are often mistaken for acneiform lesions. Ash leaf spots are less common than simple hypopigmented macules. Shagreen patches are raised plaques that are either flesh colored or yellowish brown. The surface of these lesions is bumpy. The histologic picture is that of a connective tissue nevus. The fibrous plaques are usually found on the forehead and scalp and are rubbery and yellowish brown or flesh colored. Histologically, they resemble angiofibromas. Ungal fibromas usually do not appear until after puberty.

Seizures are probably the most common presenting symptom of TS, occurring in up to 80% of affected individuals. Tuberous sclerosis is the underlying cause of infantile spasms in 10% to 15% of cases. Any child with seizures should undergo a careful skin examination, including the use of a Woods lamp, to search for cutaneous signs of TS or other neurocutaneous disorders. Mental retardation was once thought to be universally present in individuals with TS. As the spectrum of this disorder is recognized, fewer than 50% of affected individuals may ultimately demonstrate mental subnormality. The presence and degree of retardation appears to be related to the presence and age at onset of a seizure disorder.

As echocardiography has flourished, the incidence of cardiac tumors associated with TS has increased. In one series[2] of 43 children with TS, cardiac rhabdomyomata was found in 58% of subjects. More importantly, only 18% of adults had these tumors, suggesting that the tumors tend to regress in early infancy and adolescence. Symptoms of these cardiac tumors include outflow-tract obstruction, dysrhythmias, and impairment of ventricular wall contractility.

Approximately half of children with TS have kidney involvement. The most common lesions, angiomyolipomas, may be or manifest as recurrent episodes of gross hematuria, flank or lumbar pain, or renal masses. Renal cysts associated with TS may be difficult to distinguish from those of polycystic renal disease.[3]

Genetics

The pattern of inheritance of TS is consistent with an autosomal-dominant trait. More than 60% of cases may be the result of new mutations.[4] A careful study from Scotland[4] suggested a prevalence of one in 12 000 among children younger than age 10 years, making TS much more common than previously estimated.

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Pathological Case of the Month

Russell Chesney, MD, Aaron Friedman, MD (Contributors);
Enid Gilbert-Barness, MD (Contributor and Section Editor)

This 12-year-old girl had normal growth and development until age 5 years, when lethargy, nausea, vomiting, and pallor due to anemia developed. She had the features of uremia, with foul breath and facial edema. Laboratory values were as follows: serum calcium, 1.47 mmol/L; serum potassium, 5.9 mmol/L; and blood urea nitrogen, 71 mmol/L. Extensive nephrocalcinosis was evident on abdominal roentgenograms. The patient's height was 107 cm at age 5 years and failed to increase during the next 7 years (Fig 1). After 6 months of hemodialysis, the patient underwent a bilateral renal transplant. After a minor fall, a transverse fracture of the right femur at the level of the lesser trochanter (Fig 2) occurred. She was immobilized in a hip-spica cast, and her serum calcium level increased to 3.3 mmol/L. Her parathyroid hormone level was 11 mmol/L (in the normal range). A parathyroidectomy was performed in which three parathyroid glands and three quarters of a fourth parathyroid gland were removed. Multiple fractures occurred during the next several years. Oxalate crystals were evident in urinary sediment (Fig 3) and on bone biopsy (Fig 4).

Because of the severe bone disease evident on roentgenographic examination, the patient was treated with analogs of vitamin D, including 1,25-dihydroxy vitamin D, every other day while on a diet providing 480 to 520 mg of calcium daily. Within 7 days, her serum calcium level increased to 3.4 mmol/L, and her urinary calcium level increased from 83 to 153 mg/d.

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From the Department of Pediatrics, University of Tennessee, Memphis (Dr Chesney) and the Departments of Pediatrics (Dr Friedman) and Pathology and Pediatrics (Dr Gilbert-Barness), Center for Health Sciences, University of Wisconsin, Madison.

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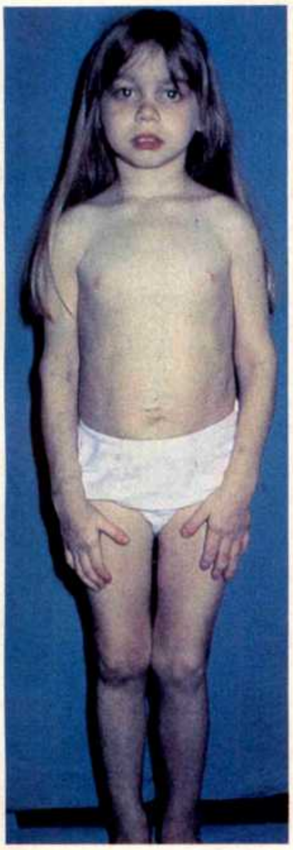

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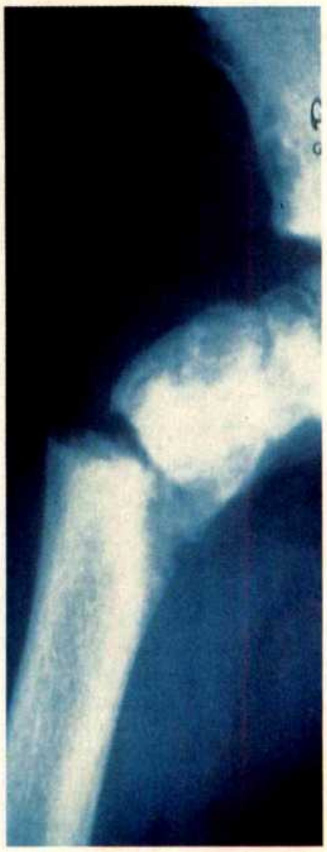

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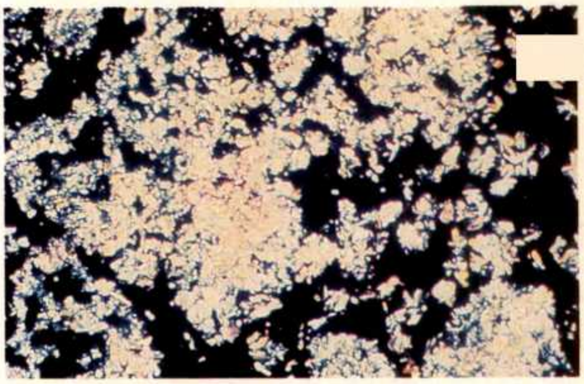

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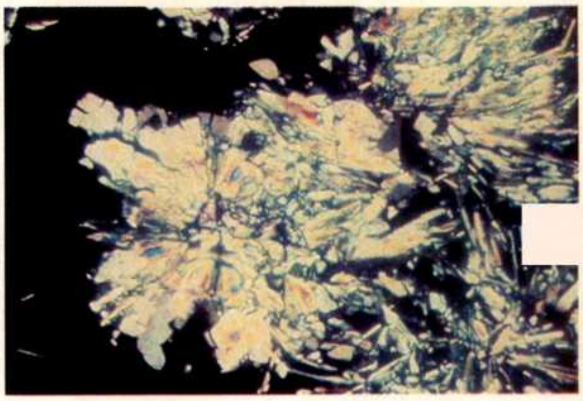

Figure 4.

Diagnosis and Discussion

Primary Oxalosis (Primary Hyperoxaluria)

Fig 1.—*The patient at age 12 years. No linear growth had occurred for 7 years.*

Fig 2.—*Roentgenogram showing fracture of the femur and osteomalacia.*

Fig 3.—*Urinary sediment viewed with polarized light showing myriad calcium oxalate crystals.*

Fig 4.—*Calcium oxalate crystals with sunburst appearance viewed with polarized light on bone biopsy (original magnification ×400).*

The nature and extent of this patient's bone disease are related to the severity of the primary hyperoxaluria. The patient had extrusion of calcium oxalate crystals into the nail beds. Multiple fractures with minimal trauma occurred in the region of the metaphyses.

The pathologic fractures seemed to resemble osteitis fibrosa cystica of hyperparathyroidism on roentgenography; however, the roentgenographic lucencies were due to areas of extensive calcium oxalate deposition.[1]

The normal calcium compound in bone is calcium phosphate as brushite, which is 15 times more soluble than calcium oxalate.[2] Hence, in a patient with unmineralized osteoid and hyperoxaluria, the deposition of calcium oxalate crystals is far more likely than the deposition of calcium phosphate in the collagen fibers of osteoid.[3] In this patient, osteomalacia is not a surprising finding; the much lower solubility of calcium oxalate prevents the precipitation of adequate calcium phosphate for normal bone formation. In areas of high concentration of calcium oxalate deposition, the preexisting bone is destroyed by osteoclastic activity. In bone, oxalate deposition is present in marrow and between bone trabeculae with wide osteoid seams (osteomalacia).[1,4]

Primary hyperoxaluria is an inborn error of metabolism transmitted as an autosomal recessive trait with extrarenal oxalate deposition. The term *oxalosis* is preferred. Two forms of primary oxalosis have been described. Patients with type 1 oxalosis have excessive urinary excretion of oxalic, glyoxylic, and glycolic acids owing to the absence of alanine:glyoxylate aminotransferase carboxylase activity, whereas patients with the much rarer type 2 disease lack D-glyceric dehydrogenase activity in leukocytes and excrete excessive oxalate and D-glycerate, but not the other acids excreted in type 1 disease.[1,5,6]

Nephrolithiasis, incomplete renal tubular acidosis, growth failure, progressive renal failure, recurrent fractures, and, frequently, cardiac arrhythmia with death before age 20 years characterize the course of the disease.[1,6-8] The calcium salt of oxalate is deposited in kidneys, bones, the conduction system of the heart, soft tissues, the central nervous system, and the rete testis. The crystals have a rosette appearance with radial striations, giving a sunburst appearance, and are best seen with polarized light. The success of renal transplantation has varied.[9,10] Successful liver transplantation seems to offer greater promise.[11,12]

Causes of secondary oxalosis include ethylene glycol and dioxane poisoning, pyridoxine deficiency, inflammatory bowel disease, methoxyflurane anesthesia, diabetes mellitus, sarcoidosis, excessive vitamin C ingestion jejunoileal bypass surgery.[13]

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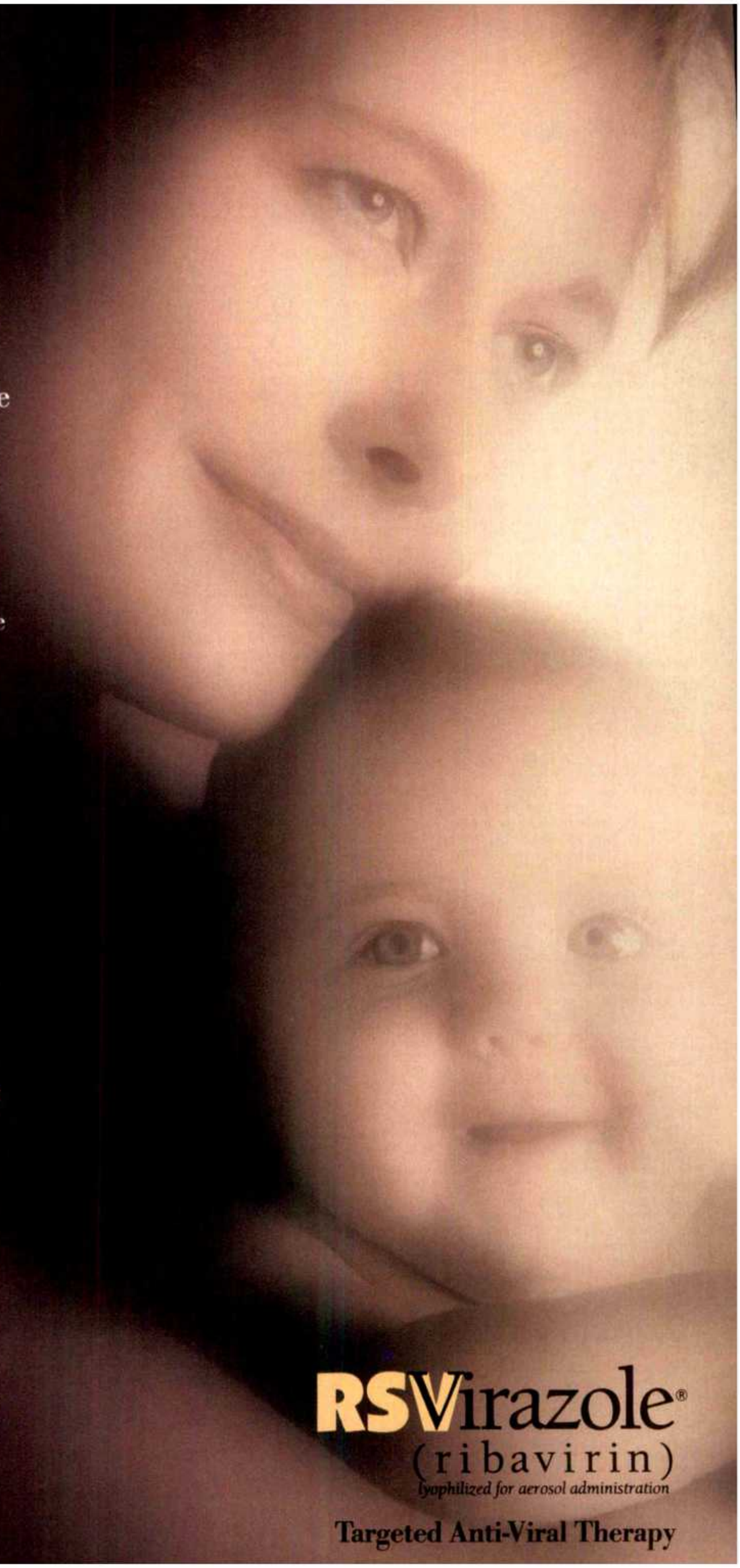

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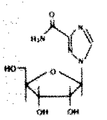
> **WARNING: RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT.** Conditions for safe use with a ventilator are still in development.
>
> Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.
>
> Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16 μg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 μM, with a mean concentration of 0.76 μM. The lasma half-life was reported to be 9.5 hours. Three ediatric patients inhaling ribavirin aerosol administered y face mask or mist tent for 20 hours each day for 5 days ad plasma concentrations ranging from 1.5 to 14.3 μM, with a mean concentration of 6.8 μM.

It is likely that the concentration of ribavirin in respiatory tract secretions is much higher than plasma concentrations in view of the route of administration. treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possible emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C3T3 cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD_{50} in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION:

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml widemouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final should not have had any antimicrobial agent or
stance added. The solution should be inspect
for particulate matter and discoloration prior
tration. Solutions that have been placed in t
unit should be discarded at least every 24 hour
the liquid level is low before adding newly re
solution.

Using the recommended drug concentra
mg/ml ribavirin as the starting solution in the
voir of the SPAG unit, the average aerosol co
for a 12 hour period would be 190 micrograms
mg/ℓ of air.

HOW SUPPLIED:

Virazole® (ribavirin) Aerosol is supplied in 1
vials with 6 grams of sterile, lyophilized drug
be reconstituted with 300 ml sterile water for i
sterile water for inhalation (no preservatives a
administered only by a small particle aerosol
(SPAG-2). Vials containing the lyophilized dr
should be stored in a dry place at 15-25°C (
Reconstituted solutions may be stored, und
conditions, at room temperature (20-30°C, 68-
24 hours. Solutions which have been placed in t
unit should be discarded at least every 24 hour

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5. Hendry RM, McIntosh K, Fahnestock ML and
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ADVERTISING REFERENCES:

1. Adapted from "Policy statement. Ribavirin
   of respiratory syncytial virus." American
   of Pediatrics Committee on Infectious D
   1986-87.

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of Pediatrics does not constitute a guar
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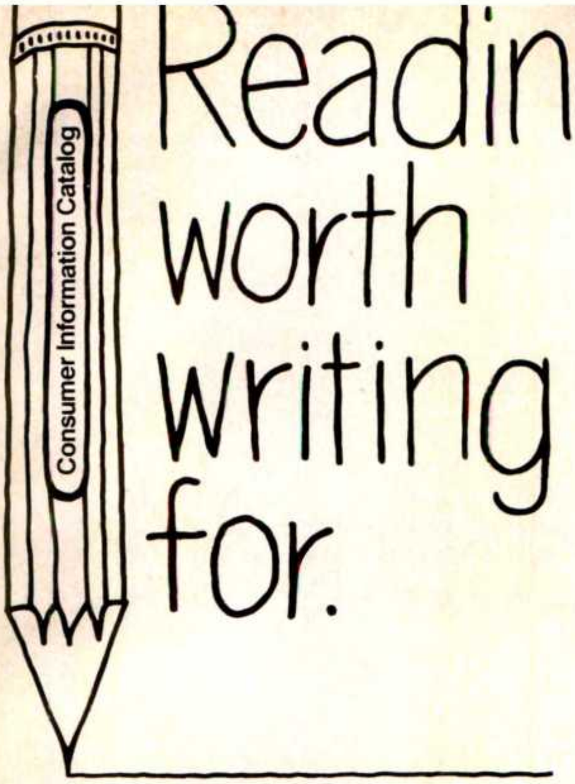

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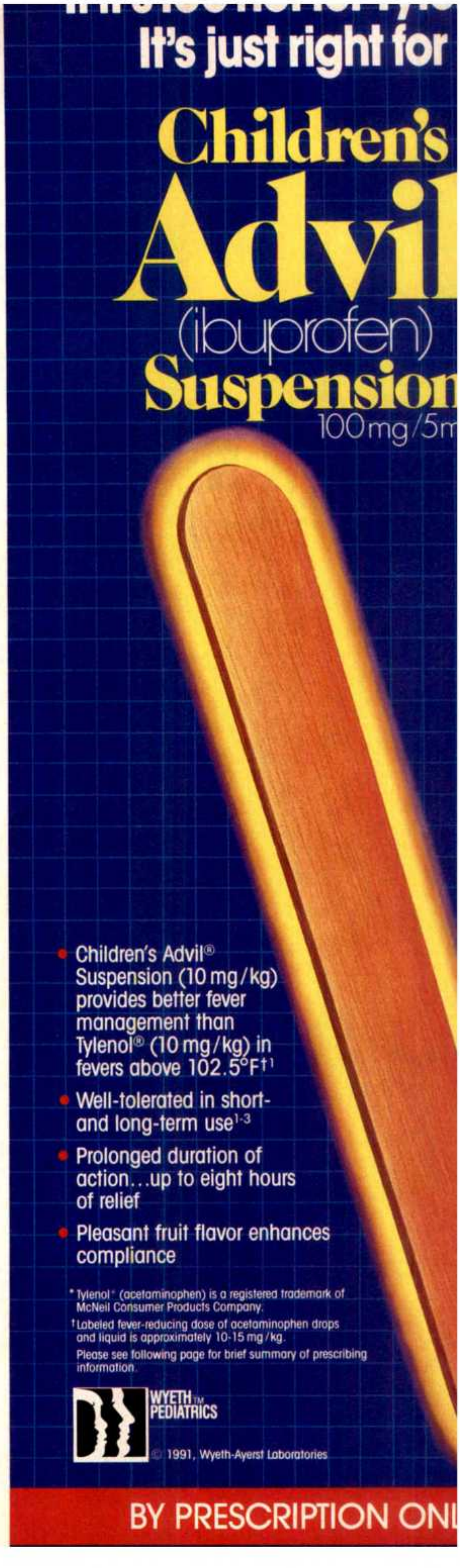

- Children's Advil® Suspension (10 mg/kg) provides better fever management than Tylenol®* (10 mg/kg) in fevers above 102.5°F†[1]
- Well-tolerated in short- and long-term use[1-3]
- Prolonged duration of action...up to eight hours of relief
- Pleasant fruit flavor enhances compliance

* Tylenol® (acetaminophen) is a registered trademark of McNeil Consumer Products Company.

† Labeled fever-reducing dose of acetaminophen drops and liquid is approximately 10-15 mg/kg.

Please see following page for brief summary of prescribing information.

WYETH™ PEDIATRICS

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Children's
Advil®
(ibuprofen)
Suspension
100 mg/5mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risks of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension. Ibuprofen can inhibit platelet aggregation and prolong bleeding time.

CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions. Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administere concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranit with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reducti renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lith toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the ag 6 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involvi chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhe epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indige nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, ves bullous eruptions; aseptic meningitis, fever and coma, confusion, depression, emotion lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotoma and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decre in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coomb's positive), neutropenia, thrombocytopenia with or without purpura; congestive heart fa in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); syndrome of abdominal pain fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearan hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Drea abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (eg., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglyce reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary nec

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should ha induced emesis or gastric lavage. Multiple dose oral administration of activated char may be useful. Supportive therapy may include oxygen, respiratory support, and pare fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children), 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

References:
1. Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989; 46: 9-17.
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References: 1. Sandler RB, et al: *Am J Clin Nutr* 1985;42:270-27 2. Rubin K: *Pediatric By-Line* 1985;4(3):1, 4-6. 3. Marston R, Rap *National Food Review* 1987;36:18-23. 4. Heaney RH: *The Physic Sportsmedicine* 1987;15:83-88.

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BUSY GROUP PRACTICE desires fifth BC/BE pediatrician. Forty-five minutes from Portland, Oregon. Excellent professional and recreational opportunities. Salary with early partnership potential. Extensive referral base. Unique hospital call system. Send CV: Dale Bartolome, MD, 784 14th, Longview, WA 98632. (206) 425-6111.

TWO BOARD-CERTIFIED pediatricians located forty minutes south of downtown Atlanta seeking third partner. New building. Extremely busy practice. Level I-II Nursery. Shared call arrangements 1:3 currently. Send CV to: Newnan Pediatrics, 58 Hospital Road, Suite 103, Newnan, GA 30263. (404) 254-8200.

UNIQUE OPPORTUNITY for BC/BE pediatrician to join busy rural practice in northwest Connecticut. Senior partner retiring after thirty years here; three others to share call. Excellent schools and hospital. Early partnership, part-time or shared position possible. CV to: Sharon Pediatrics, P.O. Box 157, Sharon, CT 06069.

PEDIATRICIAN–ANNISTON, ALABAMA

BE/BC to join established practice. Modern office and experienced staff. Nearby hospital with 372-beds. Level II Nursery. Population in surrounding area 116,034. Shared call arrangement with full call every 5th weekend. One hour from Birmingham and ninety minutes away from Atlanta, Georgia. Opportunity for full partnership. **Box #132, c/o AJDC.**

IMMEDIATE OPENING for BC/BE pediatrician to associate with well-established, rapidly growing, 32-MD multi-specialty group. Located in the San Francisco Bay area in a growing community serving 170,000. Patients include both fee-for-service and prepaid health plan. Attractive compensation and benefits. Malpractice provided. California license required. Send CV to: Bart Bona, Administrator, Fairfield Medical Group, Caller Box 4020, Fairfield, CA 94533-0410. (707) 426-3911.

PHILADELPHIA – Two pediatricians seeking BE/BC third for growing practice in southwest Philadelphia. Full partnership opportunity after two years. Send CV to: Fredric Nelson, MD, 2801 Island Avenue, Philadelphia, PA 19153.

ALABAMA/PEDIATRICIAN – BE/BC to join established practice. Modern office with experienced staff. 400-bed hospital with neonatologists and Level III NICU. Shared call arrangement, full call every 5th weekend. Community of 200,000, mild climate, lovely housing, excellent schools. Three hour drive to Florida beaches and Atlanta, Georgia. Send CV to: Robert Beshear, MD, 3401 Eastern Boulevard, Montgomery, AL 36116.

PEDIATRICIAN SEEKING BC/BE associate to join a growing practice. Malpractice coverage provided. Associated with a 350-bed general hospital and Columbus Children's Hospital. Ideal site for a young family. Please contact: P.J. Oppenheimer, MD, 1136 Independence Avenue, Marion, OH 43302.

FLORIDA – Established, progressive group in Palm Beach Gardens and Jupiter with large patient base seeks young enthusiastic well-trained pediatrician for association. Excellent arrangements for full partnership. Send resume to: Box #126, c/o AJDC.

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Send CV to:

RONALD H. DEERING, MD
Christie Clinic Association
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Champaign, IL 61820

PEDIATRICIAN

BC/BE, Pediatrician, recently trained, to join large multi-specialty group practice in Greeley, CO. Located 50 miles north of Denver, Greeley has a strong economic base, and progressive education system that includes a four-year University and a two-year Community College. The successful candidate will have immediate access to an established patient base. The practice is adjacent to North Colorado Medical Center, a regional medical facility offering a full range of medical specialties providing tertiary services to a three-state area. Candidate should have interest in general and high risk pediatrics.

Excellent practice opportunity with quality life-style. Please send CV and picture to:

Alyce M. Kantner
Director, Medical Staff Services
North Colorado Medical Center
1801 16th Street
Greeley, CO 80631

CALIFORNIA – BE/BC pediatrician to join practice which includes teaching family practice residents and private practice. Faculty appointment available. Central Valley, fast growing, moderate climate. Send CV to: Neil Ernst, MD, 315 East 13th Street, P.O. Box 231, Merced, CA 95340-0231.

PEDIATRICIAN: Five person group seeking full-time BE/BC pediatrician. Fully equipped office in Lexington, Kentucky. Nearby tertiary care residency program. Competitive salary and benefit package. Send CV: M.J. Harris, Pediatric & Adolescent Associates, 2620 Wilhite Drive, Lexington, KY 40503.

Pediatrician wanted to join an established, busy five-doctor practice.

Local S.E.C. university and good industry insures stable economic base. 300-plus bed hospital with 11-bed newly remodeled pediatric unit. Level II Nursery. Average 130 deliveries per month.

Convenient location in southeast for singles or families. Area provides excellent opportunities for culture, education and recreation, as well as state-of-the-art facilities.

Send CV to:
Box #131, c/o AJDC.

BC/BE general academic pediatricians for general pediatric position in large division of general academic pediatrics. Position will be a combination of primary care and teaching in the outpatient department and 2-3 month inpatient rotation each year. Clinical research is encouraged. Division foci include urban and international health care, adolescent medicine, child abuse, child development and behavior. Send CV to: Karen Olness, MD, General Academic Pediatrics, Rainbow Babies and Childrens Hospital, 2074 Abington Road, Cleveland, OH 44106. Case Western Reserve University is an equal opportunity/affirmative action employer.

GENERAL PEDIATRICS: The University of California, Davis, Department of Pediatrics, is seeking an academic physician who is board-certified/-eligible in pediatrics. Proven excellence in clinical care, teaching and research abilities. A subspecialty interest such as adolescent medicine or emergency pediatrics is desirable. Submit CV and the names and addresses of five references to: Dr. Dennis M. Styne, Chair, Pediatrics-2516 Stockton Boulevard, Sacramento, CA 95817. The University of California is an equal opportunity/affirmative action employer. Closes: Open until filled, not later than April 15, 1992 to be considered.

THE OHIO STATE UNIVERSITY Department of Pediatrics is seeking a board-certified/board-eligible pediatrician who has completed a fellowship in pulmonary medicine. Responsibilities include patient care, teaching and research in an academically oriented Children's Hospital. Competitive salary and benefits. Applicants should send curriculum vitae to: Karen McCoy, MD, Chairman, Pulmonary Search Committee, Children's Hospital, Inc., 700 Children's Drive, Columbus, OH 43205. The Ohio State University is an affirmative action/equal opportunity employer.

PENNSYLVANIA – BC pediatrician in north central Pennsylvania seeks BC/BE associate to join challenging rural practice. Position offers excellent salary and benefits with potential for loan repayment. Affiliated hospital has 160-beds (55 long term care), Level I Nursery, and multi-specialist physician staff. Area features a wide variety of outdoor activities, including hiking, skiing, biking, fishing, and hunting. Reply to: Jan Freeman Kinsley, Physician Recruiter, at (814) 274-0229. Or send curriculum vitae to: Charles Cole Memorial Hospital, U.S. Route 6, Coudersport, PA 16915.

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Send cover letter indicating position of inter est with CV and two letters of reference to:

L. Gregory Pawlson, MD, Chairman
Department of Health Care Sciences
Room 2B-418, 2150 Pennsylvania Ave. N
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NEW YORK – BC/BE PEDIATRICIAN to join b practice. Salary guaranteed, leading to partners Training in neonatology preferred. Fully equip offices in highly desirable location. One hour n of New York City. Send CV to: Box 128, c/o AJD

BC/BE PEDIATRICIAN NEEDED to replace ret partner in three-person department with a 27-ph cian multi-specialty group. Competitive salary incentives and benefits offered. Send CV to: M Lehman, Administrator, Elkhart Clinic, P.O. Box Elkhart, IN 46515.

Faculty Positions

ILLINOIS – Academic general pediatricians. Department of Pediatrics, Loyola University Chic Stritch School of Medicine, is seeking additi career oriented members. BC/BE pediatricians general pediatrics/fellowship experience nee Subspecialty interest welcomed. Interested a cants may send their current CV and accompan letter to: Craig L. Anderson, MD, Departmen Pediatrics, Loyola University Medical Center, 2 South First Avenue, Maywood, IL 60153. (708) 3373. Loyola University is an equal opportunity cator and employer. Qualified persons are not ject to discrimination on the basis of a handicap.

UNIVERSITY OF CALIFORNIA, Irvine, Pedi Residency Program Director – Full-time faculty p tion at Assistant/Associate Professor level in Department of Pediatrics. Board-certified/-eligib pediatrics. Responsibilities include teaching, clin service and administration. The candidate will be sponsible for coordination and management of p atric training program, curriculum development implementation and vocational counseling to r dents. Send curriculum vitae and names/addres of three references to: Deborah C. Stewart, Division of General Pediatrics, University of Cali nia, Irvine Medical Center, P.O. Box 14091, Ora CA 92613-4091. Affirmative action/equal opportu employer.

Faculty Positions

PEDIATRICIAN – Seeking BC/BE MD or DO pediatrician for full-time faculty position with clinical and academic responsibilities. Send CV to: Lawrence E. Jacobson, DO, Dean for Academic Affairs, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312.

WOMEN & INFANTS' HOSPITAL of Rhode Island is seeking a neonatologist. The successful candidate must qualify for a full-time faculty position at the rank of instructor or assistant professor at the Department of Pediatrics of the Brown University School of Medicine. Job responsibilities include: Attending as staff Neonatologist in the special care nursery at Women & Infants' Hospital; outreach, training and coverage of the newborn nursery service at an area community hospital; and conduct of clinical or laboratory research as an independent investigator. The minimum requirements are:

1. Board certified/board eligible in pediatrics and neonatal/perinatal medicine.
2. Direct and supervisory patient care experience with Level I, Level II, and Level III newborn nurseries in tertiary referral centers and community hospitals.
3. Demonstrated experience and ability in teaching and outreach in community hospital newborn services.
4. Ability and prior experience in clinical or laboratory research, preferably in areas pertaining to neonatal lung injury and lung development.

Interested individuals should send application and curriculum vitae to:

William J. Cashore, MD, Chairman
Search Committee, Department of Pediatrics,
Women & Infants' Hospital
101 Dudley Street, Providence, RI 02905.

Applications are expected by February 29, 1992. Screening will begin on that date and continue until a successful candidate has been identified or the search is closed.

Women & Infants' Hospital is an equal opportunity/affirmative action employer and actively solicits applications from members of minority and protected groups.

Residencies

PL-IV/PEDIATRIC CHIEF RESIDENT – Colorado. An opportunity exists for a chief resident for the academic year beginning June 1992. The three chief residents for this program actively supervise the function of multiple services. This is an excellent opportunity to improve teaching and organizational skills. Four months of the year is set aside for research and academic work. If interested, please send curriculum vitae to: James. V. Lustig, MD, Professor and Vice Chairman, Department of Pediatrics, University of Colorado School of Medicine, The Children's Hospital, 1056 East 19th Avenue, Box B-175, Denver, CO 80218. Or call: (303) 861-6918.

Positions Wanted

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The Search Committee of AAP invites applications for the position of

EXECUTIVE DIRECTOR, AMERICAN ACADEMY OF PEDIATRICS

James E. Strain, MD, who has been Executive Director of the American Academ Pediatrics for the past five and a half years, has tendered his resignation effective in , 1993. A search committee has been constituted to evaluate applicants for this positio

The Executive Director provides leadership and direction to the Academy and its s on a day-to-day basis and ensures that the policies of the Academy are carried out. Executive Director reports directly to the Executive Committee and to the Execu Board.

Candidates must be pediatricians and fellows of the AAP. They should have a br understanding of pediatrics. Past involvement in the Academy's activities is hig desirable.

Proven administrative and verbal skills and an ability to effectively and articula represent the Academy in a wide variety of circumstances are essential. Applicati from qualified women and minority candidates are encouraged.

The Executive Directorship is based at the AAP offices in Elk Grove Village, Illin The position entails considerable travel. Applicants should expect to devote a minim of seven to ten years to the position.

Nominations, applications and a current curriculum vi should be submitted prior to April 1, 1992 to:

Daniel Shea, MD
President
American Academy of Pediatrics
P.O. Box 368
DePere, Wisconsin 54115

Director of Pediatric Education

The Department of Pediatrics at the University of Oklahoma, College of Medicine seeks a board-certified pediatrician with special interest and experience in medical education for Director of Pediatric Education.

The department is based at the Children's Hospital of Oklahoma, a 240-plus bed teaching tertiary care medical center in Oklahoma city, Oklahoma. The primary responsibilities of this position will involve the direction of the department's entire education program with direct responsibility for the general pediatric residency program. The program currently has 36 house officers and is fully accredited by the AGME/RRC. Demonstrated abilities in teaching, clinical skills, leadership and management are required. Academic rank and salary commensurate with experience and training.

Interested candidates should forward a curriculum vitae to:

PEDIATRIC EDUCATIONAL
SEARCH COMMITTEE
c/o ALFRED W. BRANN, JR, MD
CHAIRMAN
DEPARTMENT OF PEDIATRICS
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OKLAHOMA CITY, OK 73190-3030

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References: 1. Aly R, Maibach HI. *In vivo methods for testing topical antimicrobial agents. J Soc Cosmet Chem.* 1981;32:317-323. 2. Gennaro AR, ed. *Remington's Pharmaceutical Sciences.* 17th ed. Philadelphia College of Pharmacy and Science. Easton, Pa: Mack Publishing Company; 1985:1230.

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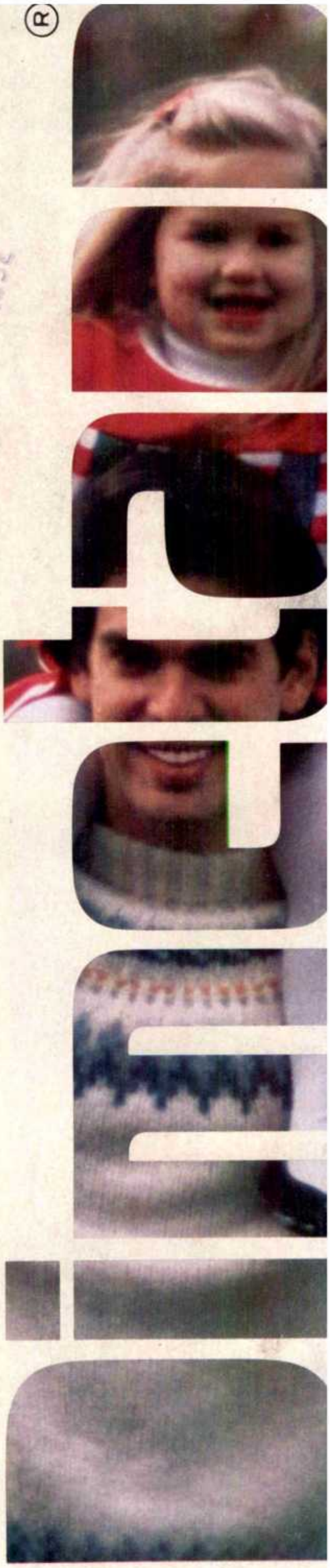

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Ambulatory Pediatric Association: Program and Abstracts

How Much 'Better' Is Good Enough? The Magnitude of Treatment Effect in Clinical Trials

T. N. K. Raju; P. Langenberg; A. Sen; O. Aldana, MD

The Efficacy of Nebulized Metaproterenol in Wheezing Infants and Young Children

A. J. Alario; W. J. Lewander; P. Dennehy; R. Seifer; A. L. Mansell

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Assessment of Otoscopists' Accuracy Regarding Middle-Ear Effusion: Otoscopic Validation

P. H. Kaleida, S. E. Stool

Volume 146, Number 4

American Medical Association

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Please see brief summary of prescribing information below for contraindications, warnings, precautions and adverse reactions. *For susceptible strains of indicated organisms. Clinical response is 96%.[1] †Augmentin® destroys β-lactamase from susceptible bacterial strains.
1. Data on file, SmithKline Beecham Pharmaceuticals.
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Augmentin®
amoxicillin/clavulanate potassium

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse* (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage and Administration: The *Augmentin* 250 mg tablet and the 250 mg chewable tablet do *not* contain the same amount of clavulanic acid (as the potassium salt). The *Augmentin* 250 mg tablet contains 125 mg of clavulanic acid, whereas the 250 mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the *Augmentin* 250 mg tablet and the 250 mg chewable tablet should *not* be substituted for each other, as they are not interchangeable.

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Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and lower respiratory tract infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Severe infections should be treated with the higher recommended dose.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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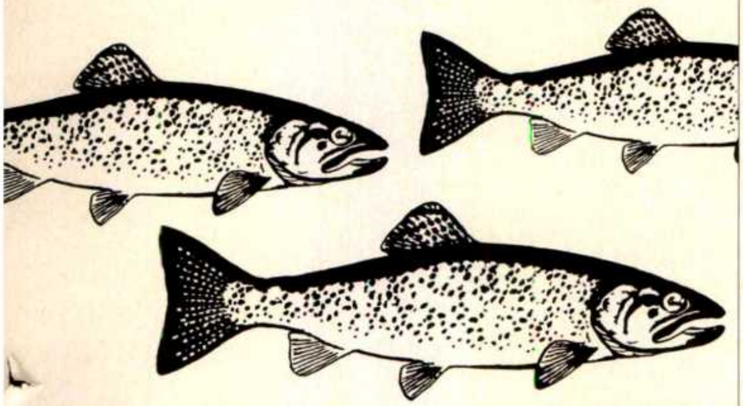

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INTAL® Inhaler, 800 mcg/puff
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Brief Summary

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were:

Throat irritation or dryness
Bad taste
Cough
Wheeze
Nausea

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

CAUTION: Federal law prohibits dispensing without prescription.

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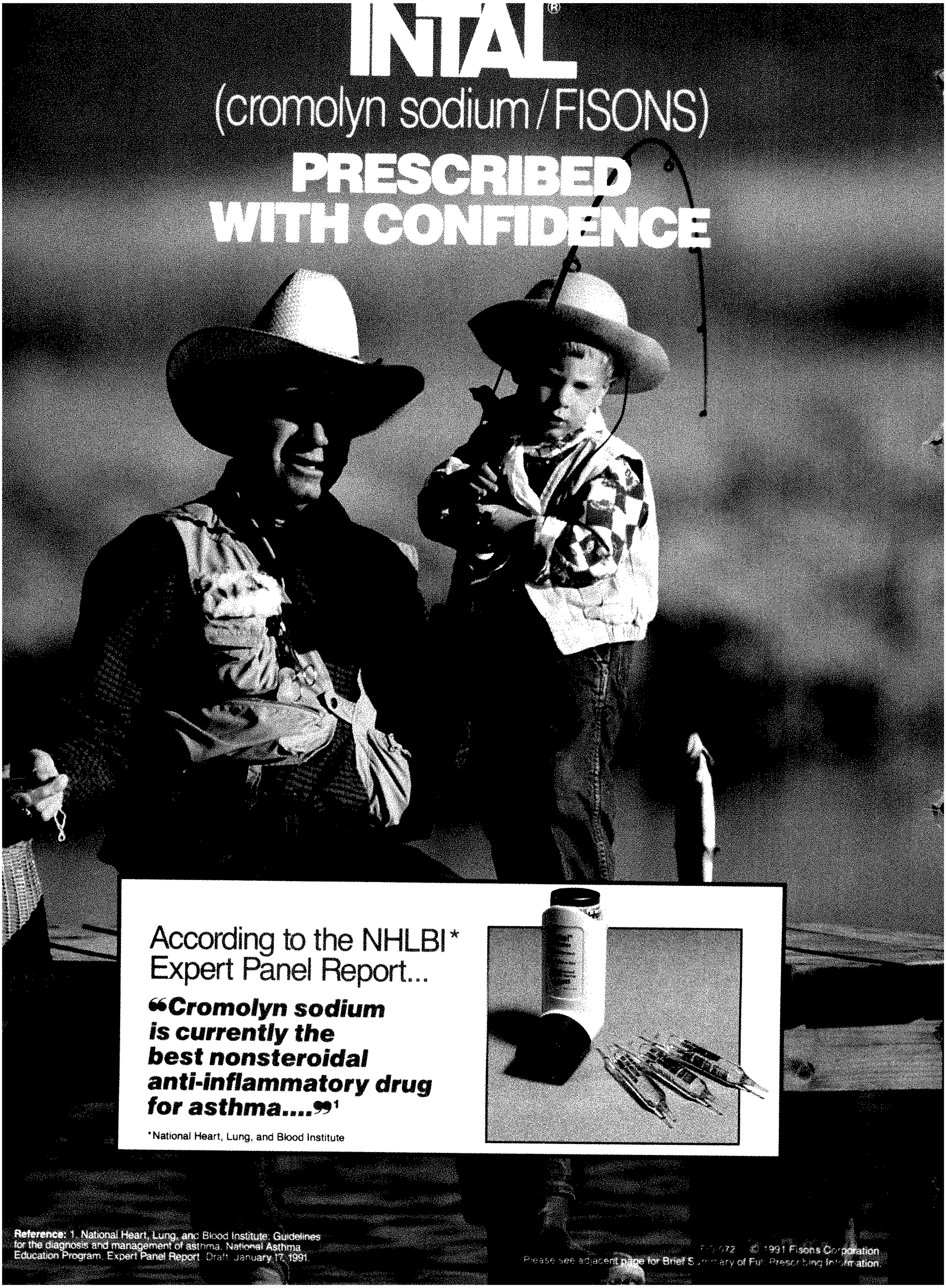

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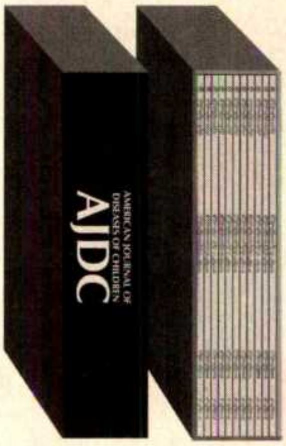

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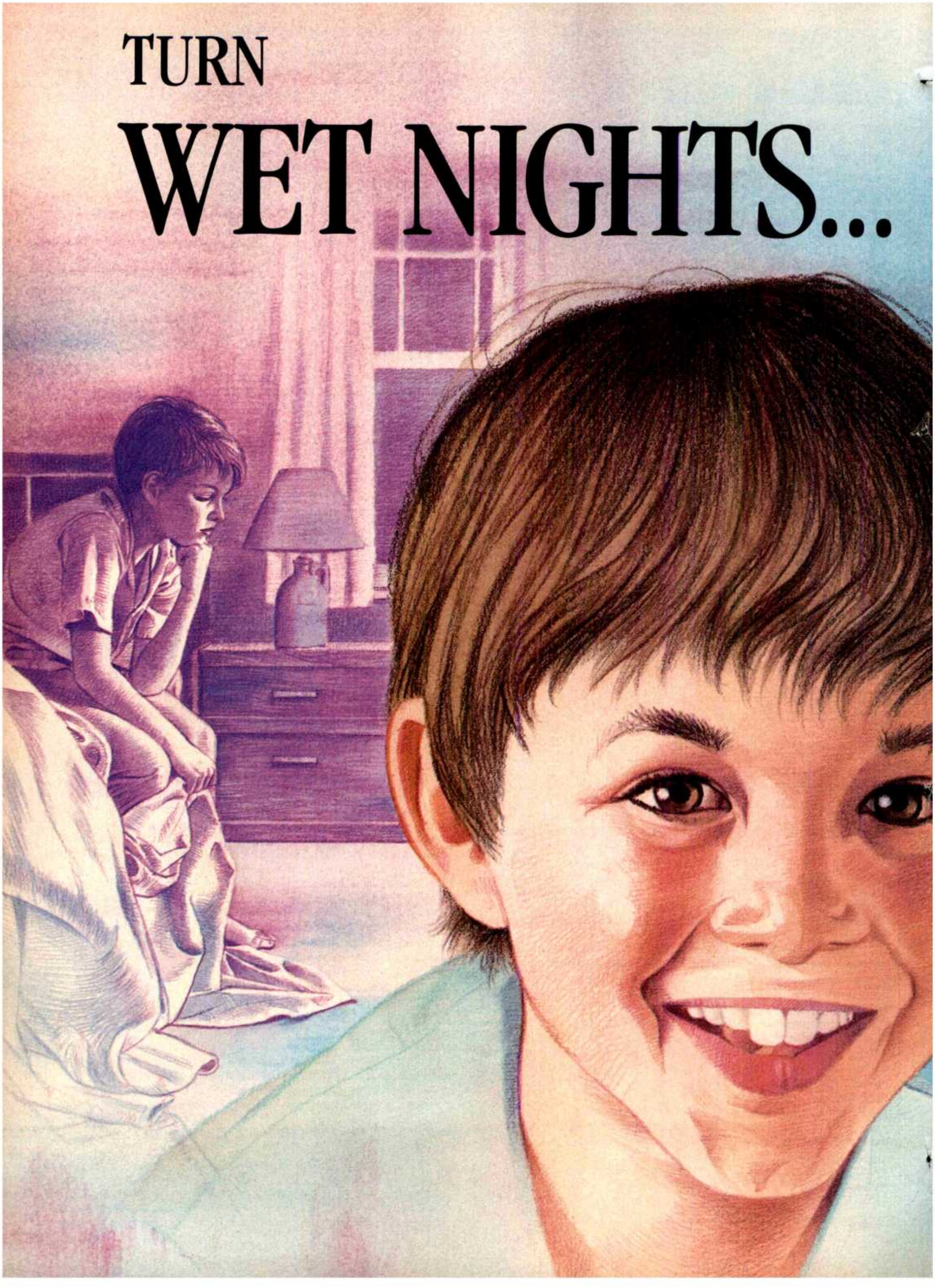
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PRECAUTIONS:
General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.
DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.
Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used. For such situations, DDAVP injection should be considered.
Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP Nasal Spray should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.
Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.
Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities. No further information is available.
Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg.
Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.
Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.
Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nose-bleed, sore throat, cough and upper respiratory infections have also been reported.
The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=59) %	DDAVP 20 mcg (N=60) %	DDAVP 40 mcg (N=61) %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see full prescribing information in product circular.

1. Dimson SB: DDAVP and urine osmolality in refractory enuresis. *Arch Dis Child* 1986;61:1104–1107. 2. Miller K, Goldberg S, Atkin B: Nocturnal enuresis: Experience with long-term use of intranasally administered desmopressin. *J Pediatr* 1989;114(4, Part 2):723–726. 3. Aladjem M, Wohl R, Boichis H, et al: Desmopressin in nocturnal enuresis. *Arch Dis Child* 1982;57:137–140. 4. Rittig S, Knudsen UB, Sørensen S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium.* England: Horus Medical Publications; 1988:43–55. 5. Post EM, Richman RA, Blackett PR, et al: Desmopressin response of enuretic children: Effects of age and frequency of enuresis. *Am J Dis Child* 1983;137:962–963. 6. Rew DA, Rundle JSH: Assessment of the safety of regular DDAVP therapy in primary nocturnal enuresis. *Br J Urol* 1989;63:352–353.

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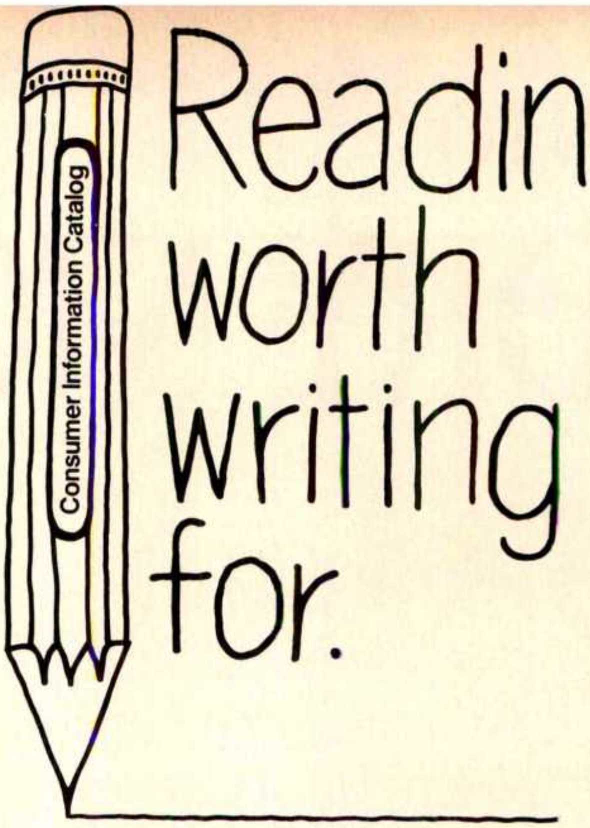

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1992 Annual Meeting

The annual meeting of The American Pediatric Society, The Society for Pediatric Research, and The Ambulatory Pediatric Association will be held May 4-7, 1992, at the Baltimore (Md) Convention Center. For further information, contact the APS/SPR Association Headquarters, 141 Northwest Point Blvd, PO Box 675, Elk Grove Village, IL 60009-0675; (708) 427-0205; Fax (708) 427-1305; or the Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101; (703) 556-9222.

1992 Pediatric Emergency Medicine Examination

The American Board of Pediatrics (ABP) and the American Board of Emergency Medicine (ABEM) will administer the first Certifying Examination in Pediatric Emergency Medicine Tuesday, November 17, in three US cities. If you are certified in General Pediatrics by the ABP or you are certified by both the ABP and the ABEM, you must submit an application to the ABP for the credentialing process. If you are certified only by the ABEM, you must submit an application to the ABEM.

Applications are available now. Registration is from February 1 through April 30. The application fee established by the ABP for the examination is $1150, but applications postmarked after March 31 must include an additional $200 late fee. Applications postmarked after April 30 cannot be accepted for the 1992 examination. The application fee has not been established by the ABEM, but it will not be less than the ABP fee; it will be announced in the application packet from the ABEM.

Each application will be considered individually and must be acceptable to the Sub-board of Pediatric Emergency Medicine. Please contact the ABP or the ABEM for eligibility requirements. Please direct inquiries to: American Board of Pediatrics, 111 Silver Cedar Ct, Chapel Hill, NC 27514-1651; (919) 929-0461; Fax (919) 929-9255; or American Board of Emergency Medicine, 200 Woodland Pass, Suite D, East Lansing, MI 48823; (517) 332-4800; Fax (517) 332-2234.

1992 Pediatric Endocrinology Examination

The American Board of Pediatrics will administer the Certifying Examination in Pediatric Endocrinology Tuesday, November 17, in three US cities.

Applications are available now. Registration is from February 1 through April 30. The application fee for the examination is $1150, but applications postmarked after March 31 must include an additional $200 late fee. New applications postmarked after April 30 cannot be accepted for the 1992 examination.

Each application will be considered individually and must be acceptable to the Sub-board of Pediatric Endocrinology. Please contact the American Board of Pediatrics (111 Silver Cedar Ct, Chapel Hill, NC 27514-1651; [919] 929-0461) for eligibility requirements.

Reregistration materials were mailed to eligible candidates on March 1. The reregistration fee is $1050.

1992 Pediatric Gastroenterology Examination

The American Board of Pediatrics will administer the Certifying Examination in Pediatric Gastroenterology Tuesday, November 17, in three US cities.

Applications are available now. Registration is from February 1 through April 30. The application fee for the examination is $1150, but applications postmarked after March 31 must include an additional $200 late fee. New applications postmarked after April 30 cannot be accepted for the 1992 examination.

Each application will be considered individually and must be acceptable to the Sub-board of Pediatric Gastroenterology. Please contact the American Board of Pediatrics (111 Silver Cedar Ct, Chapel Hill, NC 27514-1651; [919] 929-0461) for eligibility requirements.

Reregistration materials were mailed to eligible candidates on March 1. The reregistration fee is $1050.

Cat-scratch Disease: Therapy With Trimethoprim-Sulfamethoxazole

Sir.—Cat-scratch disease generally consists of regional lymphadenitis due to a gram-negative bacillus acquired from cats. There is often a small red papule or an infected scratch near the involved lymph node. Complications or other manifestations of the disease have included conjunctivitis, encephalopathy, peripheral neuropathy, osteolytic lesions, and polyneuritis. Treatment with oral trimethoprim-sulfamethoxazole was reported recently.[1] This report extends those observations.

Patients and Methods.—A retrospective review of 50 000 patient visits to a pediatric office in southeast Georgia from 1984 to 1990 disclosed the cases diagnosed as cat-scratch disease, lymphadenitis, regional lymphadenopathy, and adenitis. Patients with generalized adenopathy, bilateral adenopathy, and lymphadenopathy with splenomegaly were excluded. All patients were questioned carefully about exposure to cats at their home, their relatives' or friends' homes, or elsewhere.

Cat-scratch skin tests were applied at least 7 days after the onset of illness and the results read 2 to 3 days later by the patient's parents or the physician. In every case, carefully detailed instructions were given to parents who also observed the test results, and they were carefully questioned by the physician when their observations were reported by telephone. All doubtful test results were seen by the physician. The skin test antigen was prepared from pus obtained from a classic case in the usual manner, and it was confirmed to be sterile when cultured for viruses, aerobically and anaerobically. Children were seen for follow-up in the physician's office or reports were given by telephone. The skin test materials tested positive for cat-scratch disease bacillus DNA by the polymerase chain reaction in the laboratory of Bradley Perkins, MD, Centers for Disease Control, Atlanta, Ga. Biopsy specimens from several inoculation papules on the skin were also tested by Dr Perkins.

Results.— The ages of the 101 patients were as follows: 2 years or younger, eight patients; 3 to 5 years, 31 patients; 6 to 8 years, 33 patients; 9 to 11 years, 14 patients; 12 to 14 years, 12 patients; and 15 to 17 years, three patients. There were 53 girls and 48 boys. Ninety-nine of these patients had a definite history of exposure to cats within 2 to 4 weeks before onset of the illness, and 70 (69%) of the 101 patients had positive skin test results. The other 31 patients did not receive skin tests.

During this 6-year period another 31 children had regional lymphadenitis due to other causes as follows: cellulitis (staphylococcus and streptococcus), eight patients; viral upper respiratory infection, eight patients; mycoplasmal pneumonia, four patients; herpes stomatitis, three patients; dental abscess, two patients; infectious mononucleosis, one patient; atypical mycobacteria, one patient; and unknown, four patients. These patients were treated for the condition that was diagnosed, and the four cases with unknown diagnoses resolved without treatment. These four patients had no history of exposure to cats. All 31 children had tender lymph nodes that were 2 cm or larger in just one area of the body.

The locations of the enlarged tender lymph nodes in the 101 cases of cat-scratch disease are as follows: cervical, 31 patients; axillary, 33 patients; inguinal, 16 patients; preauricular, seven patients; submandibular, 10 patients; postauricular, two patients; supraclavicular, one patient; and epitrochlear, one patient.

Treatment Administered to Patients With Cat-scratch Disease

No. of Patients	Antibiotic (Dosage)	Outcome
71	Trimethoprim (10 mg/kg twice daily) Sulfamethoxazole (100 mg/kg twice daily)	Resolved in 5-16 d
21	Cephalexin (250 mg twice daily)	16 cases resolved in 9-28 d, 5 nodes suppurated and drained for 1-2 mo
3	Cefadroxil (250 mg twice daily)	1 case resolved in 15 d, 2 nodes suppurated and drained for 1-2 mo
1	Erythromycin (200 mg three times daily)	Resolved in 14 d
1	Cloxacillin (250 mg twice daily)	Resolved in 10 d
1	Amoxicillin and clavulanate (250 mg three times daily)	Resolved in 16 d
1	Cefaclor (250 mg twice daily)	Resolved in 10 d
2	None	Resolved in 10-14 d

The treatment for 71 children consisted of trimethoprim-sulfamethoxazole twice daily. The duration of treatment in all cases was no fewer than 7 days and no more than 16 days. Sixty-nine (97%) of the 71 children had smaller lymph nodes with reduction in tenderness or no tenderness within 10 days. One child returned after 1 week and was found to be receiving only half the medication dosage. When it was increased, the lymph node subsided within a few days.

One 10-year-old girl had been seen in an emergency department three times during the previous month with a large 3-cm tender axillary node and a 5-cm supraclavicular node, and had received oral cephalexin. The glands had increased in size and 4 mL of pus was aspirated from the supraclavicular node. She was treated with trimethoprim-sulfamethoxazole and both glands were nontender within 5 days and healed in 14 days. Results of her skin test for tuberculosis were negative, the pus was sterile, and the cat-scratch skin test results were positive.

The Table summarizes these cases and the 30 others that were managed before July 1987 when trimethoprim-sulfamethoxazole began to be used routinely. Of the 30 cases managed with other antibiotics, seven (23%) progressed steadily to larger, more tender glands, which suppurated and drained between 4 and 8 weeks after the illness began. Several of the antibiotics were only given to a single patient, and these patients improved gradually in a manner similar to the two children who received no antibiotics. The duration of tenderness and swelling was shorter and the number of patients who eventually experienced suppuration was fewer in the group treated with trimethoprim-sulfamethoxazole.

Comment.—The treatment of cat-scratch disease has been unsatisfactory until recently. Oral trimethoprim-sulfamethoxazole was reported to be effective in 11 patients in 1989, and this report extends those observations. Some patients with cat-scratch disease got better without therapy. The fact that this occurred is expected in this disease. In fact, some patients seemed to improve with cephalosporin therapy. However, patients who were not treated with trimethoprim-sulfamethoxazole sometimes developed suppurative adenitis; since trimethoprim-sulfamethoxazole has been in use none have developed this. The number of patients is large enough now to conclude that trimethoprim-sulfamethoxazole is a satisfactory therapy for this disease.

A controlled prospective clinical trial is still needed to confirm these results. Cephalosporins have not been effective, and yet are commonly prescribed. Cephalosporins are very effective in treating skin infections, abscesses, cellulitis, and lymphadenitis associated with those problems. However, in cat-scratch disease the skin infection papule or infected scratch is usually very minor in appearance, compared with the large, tender, obviously infected lymph node. When the clinical picture is like this, and there is a history of exposure to cats within the previous 2 to 3 weeks, treatment with trimethoprim-sulfamethoxazole in adequate doses is routinely effective.

From 1984 to 1990 (50 000 office visits) there were 101 cases of cat-scratch disease and 31 cases of regional lymphadenitis due to other causes. The most common cause of regional lymphadenitis seen here has been cat-scratch disease. The other cases were usually associated with additional findings that made cat-scratch disease unlikely. Such findings included an obvious upper respiratory infection, abscess or wound nearby, a dental abscess, and mouth ulcers. There were no cases with neurologic manifestations or osteolytic lesions, which are uncommon additional manifestations of the disease.

Other treatments recently proposed have included oral ciprofloxacin (given to five adults with the disease),[2] parenteral gentamicin,[3] and oral erythromycin in cat-scratch disease associated with acquired immunodeficiency syndrome.[4] Several excellent reviews of cat-scratch disease have been published recently.[5-7]

Seventy-one patients with cat-scratch disease were successfully treated with oral trimethoprim-sulfamethoxazole. These were compared with 30 children treated with cephalosporins and other antibiotics. All 71 children in the first group healed promptly and there was no suppuration or drainage from the nodes. Of the 30 children in the second group, seven had nodes that suppurated and drained after 1 to 2 months and painful lymph nodes that persisted longer. In 50 000 office visits during a 6-year period, there were 101 cases of cat-scratch disease and 30 cases of regional lymphadenitis due to other causes.

PLATON J. COLLIPP, MD
176 Memorial Dr
Jesup, GA 31545

Reprint requests to 176 Memorial Dr, Jesup, GA 31545 (Dr Collipp).

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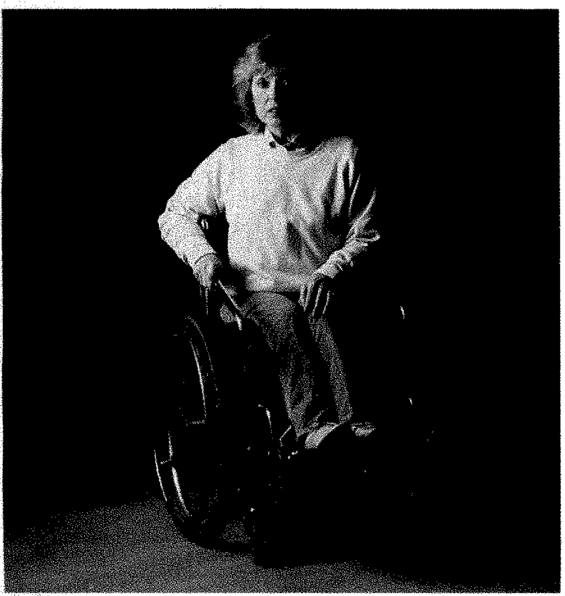

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Brief Summary

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INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*

CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in human immunodeficiency virus (HIV) infection, thymic abnormalities, leukemia, lymphoma, generalized malignancy or advanced debilitating conditions, or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. ORIMUNE should also not be given to members of a household in which there is a family history of immunodeficiency until the immune status of all members is determined to be normal. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any febrile illness or acute infection and in those with any advanced debilitated condition or persistent vomiting or diarrhea, or suspected gastroenteritis infection.

Other viruses (including poliovirus and other enteroviruses) may compromise the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis. **Records Required by the National Childhood Vaccine Injury Act:** Manufacturer and lot number of vaccine administered must be recorded by health care provider in vaccine recipient's permanent record, along with date of administration and name, address, and title of person administering vaccine.

Health care provider must report to a health department or to the FDA the occurrence following immunization of any event set forth in the Vaccine Injury Table including: paralytic poliomyelitis — in a nonimmunodeficient recipient within 30 days of vaccination — in an immunodeficient recipient within 6 months of vaccination; any vaccine-associated community case of paralytic poliomyelitis; or any acute complication or sequela (including death) of above events.

Use in Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with Poliovirus Vaccine Live Oral Trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. A large retrospective study suggests that OPV may be temporally associated with Guillain-Barré syndrome. A causal relationship has not been established. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts.

The Centers for Disease Control report that during the years 1973 through 1984 approximately 274.1 million OPV doses were distributed in the US. During this same period, 105 vaccine-associated cases were reported (1 case per 2.6 million doses distributed). Of these 105 cases, 35 occurred in vaccine recipients (1 case per 7.8 million doses distributed), 50 occurred in household and nonhousehold contacts of vaccinees (1 case per 5.5 million doses distributed), 14 occurred in immunodeficient recipients or contacts, and 6 occurred in persons with no history of vaccine exposure, from whom vaccine-like viruses were isolated.

Thirty-three (94%) of the recipient cases, 41 (82%) of the contact cases, and 5 (36%) of the immune deficient cases were associated with the recipient's first dose of OPV. Because most cases of vaccine-associated paralysis have occurred in association with the first dose, the CDC has estimated the likelihood of paralysis in association with first v subsequent doses of OPV, using the number of births during 1973-1984 to estimate the number of first doses distributed, and subtracting this from the total distribution to estimate the number of subsequent doses distributed. This method estimates a frequency of paralysis for recipients of 1 case per 1.2 million first doses v one case per 116.5 million subsequent doses; for contacts, one case per 1 million first doses v one case per 25.9 million subsequent doses; with an overall frequency of 1 case per 520,000 first doses v 1 case per 12.3 million subsequent doses.

Other methods of estimating the likelihood of paralysis in association with OPV have been described. Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults 2 doses of enhanced potency IPV a month apart before the children receive ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the second dose of enhanced potency IPV. A booster dose of enhanced potency IPV can be given to partially immunized adults at the same visit that the first dose of OPV is given to the child. The adult should be informed of precautions, such as handwashing after changing diapers.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults…[with IPV]…before giving OPV to the child."

The American Academy of Pediatrics and the American College of Physicians have made similar recommendations.

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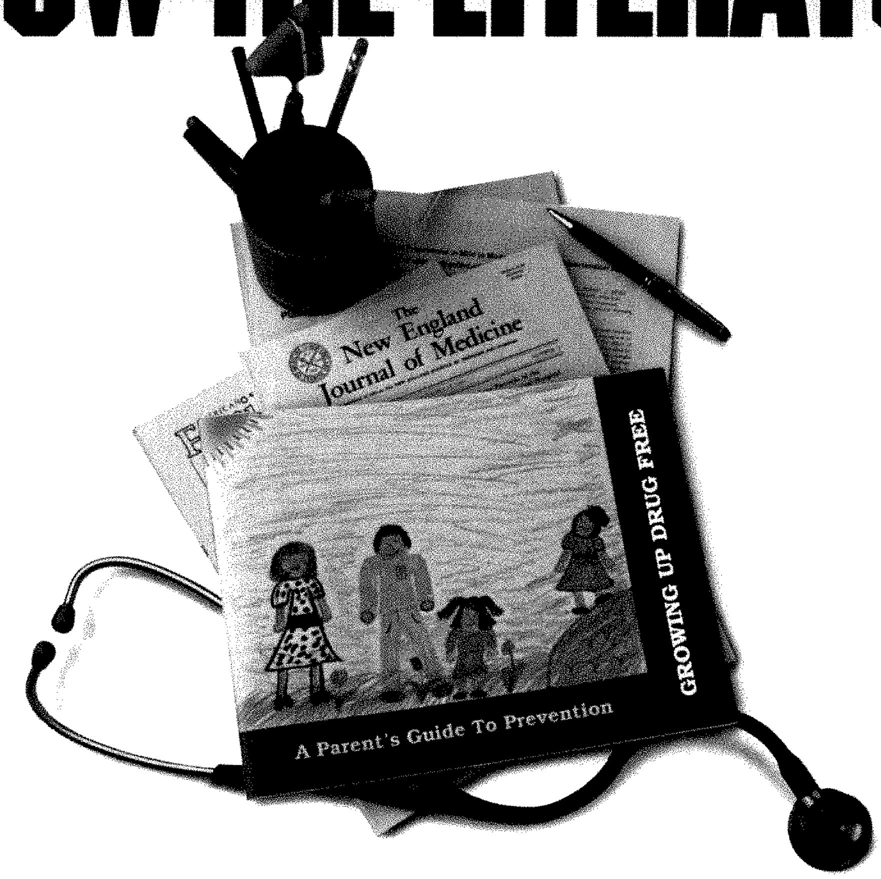
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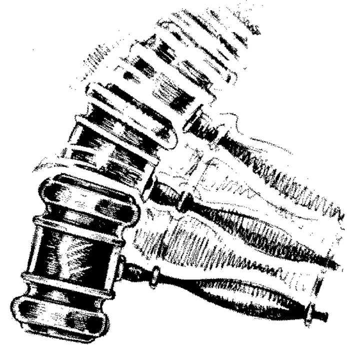

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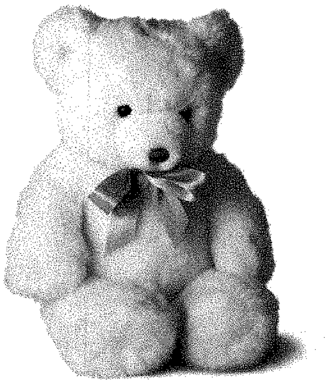

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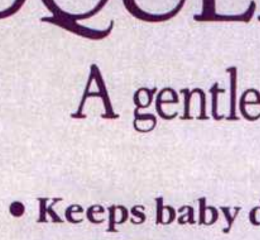

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How Much 'Better' Is Good Enough?

The Magnitude of Treatment Effect in Clinical Trials

Tonse N. K. Raju, MD; Patricia Langenberg, PhD; Ashish Sen, PhD; Otto Aldana, MD

• *Objectives.*—Among the various factors required to calculate sample size for clinical trials, the magnitude of treatment effect anticipated is an important component. The objective of this report is to present some of the complexities involved in selection of treatment effect size in clinical trials. As a framework for discussion, an analysis of published reports related to surfactant therapy was carried out.

***Design.*—Twenty-one consecutive exogenous surfactant trials for neonatal respiratory distress syndrome were analyzed. The "Methods" sections were reviewed for evaluating various components of sample size calculation, including the anticipated treatment effect size.**

***Results.*—Sixteen (76%) of the 21 reports provided a description of sample size calculations, and 12 of these gave some reasons for the choice of the anticipated treatment effect size. Expressed as percent change, the median treatment effect from intervention anticipated by the investigators was 50% (range, 15% to 90%), with a positively skewed distribution. The actual median percent reduction in adverse events from treatment (as compared with baseline) was 36% (range, 75% reduction to 5% excess). When the treatment effect was expressed as difference in adverse event rate, in the 14 (of 16) trials that could be analyzed, the median observed reduction in adverse events (death, bronchopulmonary dysplasia, or occurrence of respiratory distress syndrome) was 14.5% (range, 52% reduction to 2% excess). All trials except one concluded, however, that the intervention was effective, mostly based on additional subgroup calculations.**

***Conclusions.*—Researchers often select sample sizes capable of detecting only large treatment effects, thus risking type II error, although sometimes a much smaller effect could be clinically important. While pragmatic considerations must be considered during the design of randomized clinical trials, researchers ought to present a rationale for anticipating a given magnitude of treatment effect in their sample size calculations. It may be possible to consider innovative trial designs that help determine the most appropriate treatment choice with the least possible sample size.**

(*AJDC.* 1992;146:407-411)

Four factors are required in the calculation of sample size for clinical trials where the outcome is dichotomous: (1) the incidence for the outcome of interest; (2) acceptable level of α error probability; (3) acceptable level of β error probability; and (4) the magnitude of the treatment effect one expects from the trial.[1] The values selected for these factors influence the estimated sample size. A low event rate, low α and β values, and small effect to be detected demand a large sample size, while a smaller sample size would suffice if the converse of the above were true. With the specification of the above components by the researcher, an estimate of the sample size required can be calculated (Appendix).

The incidence for the outcome of interest might be obtained either from the published literature or personal experience. The appropriate choices for error probabilities are debated; however, most researchers choose between 1% and 5% α *error probability*: the chance of erroneously rejecting the null hypothesis (eg, incorrectly concluding two groups to be significantly different). Most researchers also choose between 5% and 20% β *error probability*: the chance of erroneously accepting the null hypothesis (eg, concluding two groups not to be significantly different when in fact they are).

How small a treatment benefit would influence a clinical decision in favor of the new treatment under study? A response to this question yields a value for the size of treatment effect "worth" detecting in the trial, the fourth component specified above. Although pilot studies can provide estimates of actual treatment effect size, the benefits of therapy must also be weighed against the cost and risks of intervention; thus, many practical, ethical, and financial issues need to be resolved in setting the treatment effect factor. Therefore, the treatment effect factor selected will vary from trial to trial. The choice of a value for this factor is not a statistical one, but rather a clinical, economic, and ethical one. This factor must be considered not merely a statistical variable whose value is to be substituted into the formula; rather, it can be thought of as a bridge between statistical procedures and clinical decision

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Read in part before the annual meeting of the Society for Pediatric Research, Anaheim, Calif, May 9, 1990.

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making. For this reason, there are no specific guidelines regarding the choice of this factor, nor can any be expected.

Because they are seldom discussed in the pediatric literature, we addressed these issues as they were relevant to recent pediatric trials. Our objectives were (1) to evaluate the size of treatment effect considered plausible by researchers in a group of published clinical trials; (2) to examine how well the choices are justified in the published articles; and (3) to review the intricacies of selecting the treatment effect size factor in the design of clinical trials.

Our intent was not to criticize the published trials but to raise scientific, ethical, and research cost questions related to this issue. This is particularly important because statistical tests generally favor the conservative treatment unless new treatments demonstrate a high level of improvement, often higher than likely to be detected with the selected sample size.

MATERIALS AND METHODS

As a framework for discussion, we reviewed artificial surfactant trials for neonatal respiratory distress syndrome (RDS). The reports were identified from the *Index Medicus* (from 1980 through 1984) and from MEDLINE computer search (1985 through 1991). We included for analyses those studies that were prospective, placebo-controlled, randomized trials that were not previously published. The "Methods" sections of the reports were reviewed to ascertain the assumptions made in determining sample size. We noted the chosen treatment effect size factors and the study end points. We computed descriptive summary measures (medians, since data were skewed, and ranges) for various components of sample size calculation and for outcome analyses. We calculated the mean differences in the observed adverse event rates and their 95% confidence intervals[2] (Appendix). Additionally, we computed the percent change (PC) in the adverse event rates as compared with baseline (control) rates as follows: $(p_t - p_c) \times 100/p_c$, where p_t and p_c are the proportions of adverse outcome in the treated and control groups, respectively. Note that these are readily converted to relative risk (RR) of adverse effect under treatment as compared with control by the formula, $RR = PC/100 + 1$.

RESULTS

To our knowledge, 38 surfactant trials were published in the English literature between January 1980 and July 1991. The characteristics of the studies analyzed are detailed in Table 1. Seventeen of these were excluded for the reasons given; 16 trials were multicenter, and five were conducted in single centers (a list of 21 studies analyzed will be provided on request). The end points selected were death or bronchopulmonary dysplasia (10), RDS (four), improvement in the ratio of arterial to alveolar PO_2 (three), death (two), bronchopulmonary dysplasia (one), and nonspecific multiple end points (one).

In 16 (76%) of 21 trials, sample size calculations were described, including a mention of the anticipated treatment effect size. In two others, only minimal details were given, and in the remaining three, no mention of sample size was made. In the 16 trials providing sample size calculations, the median required sample size was 120 (range, 26 to 440), and the median randomized reported sample size was 149 (range, 27 to 797). In all except one study, the chosen level of α error was 5% (Table 2). The choice for β errors ranged between 3% and 26%.

Table 1.—Characteristics of Reports Reviewed

Surfactant trials published	**38**
Excluded	**17**
Duplicate reports*	7
No placebo group	3
Incomplete outcome data	3
Not randomized	2
Early termination	2
Included in analyses	**21**
Natural surfactant prophylaxis	6
Natural surfactant rescue	8
Synthetic surfactant prophylaxis	4
Synthetic surfactant rescue	1
>1 treatment strategy†	2

*Preliminary reports, or conference proceedings that were later published as full-length reports.

†In these trials, the effects of both rescue and prophylactic natural surfactant therapy were investigated. Data from rescue arm of the studies were utilized for analyses of outcome.

Table 2.—Analysis of Sample Size Variables

Variables	Studies Providing Sample Size Calculations	All Studies
α Probability, %		
Median	5	5
Range	1 to 5	1 to 5
No.	16	18
β Probability, %		
Median	15	10
Range	3 to 26	3 to 26
No.	16	18
Anticipated treatment effect, % change		
Median	-50	. . .
Range	-90 to -15	. . .
No.	16	. . .
Actual % change in adverse events compared with control		
Median	-36	-29
Range	-75 to 5	-75 to 27
No.	14*	19*
Adverse event rate difference, %†		
Median	-14.5	-13.5
Range	-52 to 2	-52 to 2
No.	14*	19*

*In the remaining two reports, the outcome end points were presented only as diagrams without numeric data.

†Adverse event rate difference is an algebraic difference in adverse outcome percentage between treated and control groups. For this analysis, the adverse events were respiratory distress syndrome, bronchopulmonary dysplasia, and/or death identified as study end points by the investigators for calculation of sample size.

The median magnitude of treatment effect anticipated by the investigators, reduction in the adverse outcome, was 50%, with a positively skewed distribution and a wide range. In 12 of 16 reports, some rationales for selecting various factors needed in calculating sample sizes were given. These were mostly concerned with incidences of the outcome variables under study. The rationales for the anticipated magnitude of treatment effect cited were (1) "from past experiences" with no other details in five reports; (2) published studies in five reports; (3) from literature review in one report; and (4) a consensus obtained among the research team members in one report.

The actual median percentage reductions in adverse outcome following intervention compared with the baseline rates were lower than the anticipated median values, and the range was wide (Table 2). In eight (50%) of 16 reports, a 50% or greater treatment benefit was anticipated following intervention, but in only three (21%) of 14 reports was the treatment effect consistent with 50% or greater reduction in the proportion of adverse outcome following study intervention. (In the two remaining trials the treatment effect could not be computed.) In 17 (81%) of all 21 trials analyzed, the magnitude of observed treatment benefit was 50% or less.

The median value for the event rate differences in the adverse outcomes following treatment was only 14.5%, and the range was wide (Table 2). We also calculated 95% confidence intervals for the difference in event rates following treatment in 14 of 16 trials that described sample size calculation (Figure). These intervals were wide for most of the trials, implying that the sample sizes were generally small. All except one of 21 reports concluded that the therapy was useful, mostly based on subgroup analysis.

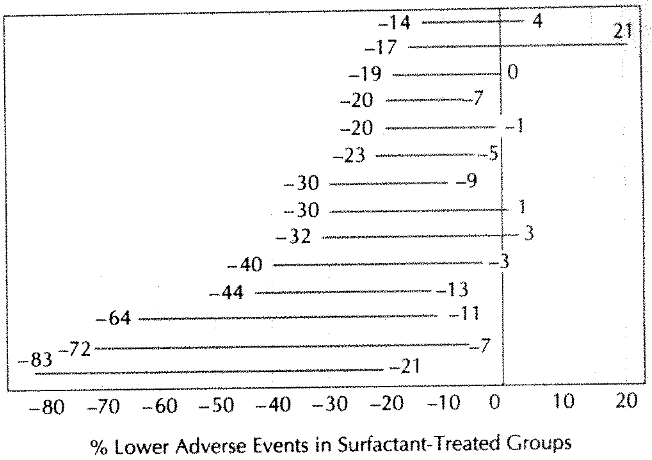
COMMENT

In contrast to other therapeutic strategies, the surfactant trials of the 1980s represent a set of remarkably well-done studies that have ushered in a new era in the management of neonatal RDS.[3,4] Therefore, our intention in this study was not to criticize either these trials or the statistical procedures they adopted. Although 19% of the trials did not provide sample size calculations, the authors of the remainder did use standard statistical procedures to derive the required sample sizes.

We believe, however, that sometimes investigators may be unaware of all the implications involved when they select an expected treatment effect size to be "plugged" into a formula for sample size. While mathematically it is only one of the factors to be considered, the choice of a value for this factor has major ethical, economic, and clinical implications. In this regard we should look on treatment effect size as a bridge between the nonstatistical and statistical aspects related to the design of clinical trials. In the discussion that follows, we will address but two issues concerning the choice of treatment effect size, with a specific focus on the trials analyzed, and a general focus on similar trials.

Large and Small Treatment Effects

In the majority of studies we analyzed, a large treatment effect was anticipated, and the intervention was found to be effective, despite small sample sizes. What is wrong then? Many of the trials risked type II error: if the true treatment effect was substantial but not so large as anticipated, there was a real risk of erroneously concluding that the intervention was not superior to the conventional therapy. Implicit in the choice of a large treatment effect size may be a notion that effects of lesser magnitude are of no consequence, so to risk missing them would not matter. Missing a clinically important effect is a well-recognized risk when one chooses a small sample size in a trial. Because some of the trials were early exploratory studies, the investigators might have been forced to choose a small sample size owing to budgetary restraints. However, such constraints were not discussed in the articles.



Treatment effect noted. The 95% confidence intervals for the adverse event rate difference following therapy are plotted for the 14 of 16 trials that described sample size calculation in their reports. In two, the outcome end-point calculations could not be done because they were presented only as diagrams.

However, sometimes one might deliberately opt to design a study only if the expected benefits from it are large and far outweigh side effects. When the cost or risk of a new therapy is considerable, or when the long-term complications from intervention are likely to be high (or unknown), one would follow such a course. Neonatal extracorporeal membrane oxygenation (ECMO) therapy is a recent example of such an approach. If only 10% more infants survive following ECMO compared with the conventional therapy, we should be more cautious in adopting this new treatment, unless the procedure is mostly risk free. In this regard, it may be worth considering the innovative (if controversial)[5] design used by O'Rourke et al[6] for ECMO therapy, where the investigators carefully weighed the risks involved with ECMO and attempted to obtain meaningful answers with the least number of patients enrolled.

However, in other conditions, even a small benefit could be worth detecting, particularly in situations where the disease has high incidence or has high associated mortality and morbidity, or when the intervention is inexpensive and relatively harmless. A modest reduction in the incidence of the common cold could have a substantial impact on national economics; a minimal reduction in arthritis pain for a bedridden person could make him or her ambulant; a 15% increase in the survival rate in patients with a malignant disease associated with high mortality could, indeed, be clinically meaningful; examples are situations where small treatment effects may be of clinical or economic significance. Following the same argument, a 25% reduction in mortality from RDS, or the incidence of bronchopulmonary dysplasia, could also have a substantial impact on neonatal care.

There is a dilemma here. One needs a large sample size, perhaps a collaborative project, to demonstrate a small treatment effect. Not many researchers have either the funding or the patient base to organize large-scale studies, possibly preventing them from testing innovative hypotheses! Therefore, many pilot studies are designed mainly to establish efficacy of intervention with limited budget and other restrictions, forcing selection of small sample sizes or of only such trials that are likely to have very large treatment effects. In this regard, let us consider the recent history of surfactant trials we analyzed in this report.

The eight studies published between 1980 and 1987 (before drug manufacturers began sponsoring the studies) were much different from the 13 that were published later. Only two of eight earlier trials were multicenter, and the median sample size was 52; in six of these trials the sample sizes were less than 100 subjects. By contrast, 10 of 13 trials published between 1988 and 1991 were multicenter, and the median sample size was 158 subjects; 11 of these had sample sizes of 100 or more, and the highest was 797. Clearly, the large treatment effect seen in earlier pilot trials provided an impetus for multicenter trials, and noncommercial and commercial agencies sponsored these studies. This example demonstrates some of the realities involved in sample size selection and the complex process leading to establishment of a therapeutic modality as standard practice. Unless the treatment effect is substantial, the researchers' level of enthusiasm to pursue further studies would be low, and the drug manufacturers' incentive to fund them might disappear. With respect to the surfactant trials, however, the therapeutic effects were indeed impressive, and hence the drugs underwent rigorous testing in a relatively short time; now this therapy has been firmly established as one of the standard treatments for neonatal RDS.

The Ethics of Controlled Trials and Cost of Knowledge

It is unethical to offer a therapy that is not beneficial, but is it also unethical to conduct a trial when the investigator anticipates the size of the treatment effect to be large? Because our pilot surfactant trial postulated a 75% reduction in adverse outcome with therapy,[7] Gore[8] was critical of it; she felt that parents ought not to consent to randomization to the placebo group if such a large effect was indeed plausible, rather than being the "most optimistic guess." If we knew that surfactant was better than placebo, irrespective of the magnitude of treatment effect, could we ethically conduct the study at all? The question is a legitimate one, but without data acquired in a scientific manner, how can we be certain that surfactant is better?

The principal issue is one of the cost—both monetary and risk of mistreatment—of acquiring information. Let us consider two treatments, A and B, where B is traditional. If the researcher knows that A is better than B, he cannot ethically assign anyone to B. If the researcher is unsure at the beginning of the study, but observes mounting evidence in favor of treatment A (particularly where the study cannot be "blinded"), at what point does it become unethical to allow a patient to be randomized? One solution may lie in using more flexible research designs that could be helpful in setting ethical and statistically sound stopping points.

One class of flexible designs that have been offered as an alternative to fixed sample size designs is the set of sequential designs. In sequential procedures, individual subjects are assigned to experimental and control groups sequentially and decisions on allocation and/or termination of the study are based on the outcomes of patients already entered. Such designs have the disadvantage of sometimes terminating a study before a statistically firm inference can be made. Furthermore, they are appropriate only in cases where the outcome can be ascertained relatively quickly.

Group sequential plans combine some of the best features of fixed-sample and sequential designs. They provide for monitoring at scheduled intervals, allowing for stopping the study when sufficiently strong evidence is observed in favor of one of the treatments. Ordinarily, the evidence in favor of one treatment must be overwhelmingly strong to stop after only a small number of patients have been accrued. Few sequential or group sequential designs have been used in pediatric studies, or for that matter in any clinical trials, so that the benefits and limitations of such designs are yet to be fully explored in application. However, there is a great deal of statistical literature on the subject.[9-11]

The Limitations of Our Study

We have compared a variety of surfactant preparations (synthetic, natural from many sources) and treatment strategies (prophylactic, rescue, single and multiple doses) spanning nearly 11 years of research. Therefore, the surfactant treatment effects presented herein should not be considered as a "metaconclusion." (Refer to other excellent reviews[4] on this subject.) Also, this report does not deal with all aspects of sample size calculation; therefore, we have not discussed other factors known to influence sample size, such as the choice of single vs two-sided tests and α and β probability levels, the prevalence (and its variability) of the adverse outcome of interest. Although we have only chosen studies with dichotomous outcome variables, the principles discussed herein would also apply to studies involving continuous and ordinal variables. In the case of continuous variables where variance is unknown, the anticipated treatment effect to be detected may be expressed in units of SD.

In summary, in this article we have highlighted a complex issue not frequently discussed in pediatric literature, namely, the choice of treatment effect size. For the novice in this field, we suggest the following outline for consideration in designing clinical trials.

1. The choice of treatment effect size for sample size calculation should depend on characteristics of the disease and the therapy. The intent of a randomized clinical trial is not necessarily to find an effect, however small it is. Rather, one must decide how good a therapy needs to be to influence clinical practice. This estimate will serve as a starting point in selecting the treatment effect size that would be worth detecting from intervention.
2. Because complex ethical, economic, and pragmatic issues are involved in determining the appropriate value for the treatment effect size, researchers planning randomized clinical trials ought to consider them during the trial design stages and provide a description of the rationale for their choices in their reports. It may be useful to specify the reasons for considering a treatment effect size in the "Methods" sections of studies.
3. For studies with acute end points, choosing innovative sequential or group sequential designs may resolve some of the ethical issues raised in sample size calculation.

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APPENDIX

Sample Size Calculation Formula

The sample size N required for each treatment arm in a clinical study involving a dichotomous outcome variable, and having a significance level α and the power $1-\beta$ to detect a true difference of at least δ between the event rates, can be estimated by the formula:

$$2N=\frac{2[Z_{1-\alpha}\sqrt{2\overline{p}(1-\overline{p})}+Z_{\beta}\sqrt{p_c(1-p_c+p_t(1-p_t))}]^2}{(p_c-p_t)^2}$$

where $2N$ is the total sample size for the study; p_c and p_t are proportions of outcome of interest in the control and the treatment groups, respectively; $p=(p_c+p_t)/2$; and $Z_{1-\alpha}$ and Z_β are the critical values to be obtained from conventional normal tables. This formula is appropriate where the total sample size is large, and when Np and $N(1-p)$ are greater than or equal to 5; the formula holds for one-sided tests. Substitute $\alpha/2$ for two-sided tests. Note that Z_β will be negative.

Confidence Interval (CI) for the Differences Between Two Proportions

The $(1-\alpha)100\%$ CI for the differences between two proportions in two unpaired samples can be constructed by first computing the SE of the difference (SE_{diff}) by the formula:

$$SE_{diff}=\sqrt{\frac{p_t\times(1-p_t)}{n_t}+\frac{p_c\times(1-p_c)}{n_c}}$$

where p is the proportion of responders; n is sample size; and the subscripts t and c refer to treatment and control groups, respectively.

The $(1-\alpha)100\%$ CI for the difference in proportions is given by[2] $(p_t-p_c)-(Z_{1-\alpha}/2\times SE_{diff})$ to $(p_t-p_c)+(Z_{1-\alpha}/2\times SE_{diff})$. This formula is a good approximation only for sufficiently large samples, and when Np and $N(1-p)$ are greater than or equal to 5.

Example

Assume the response rates to be 38 (60%) of 60 in the treatment group and 23 (38%) of 60 in the control group. The respective proportions would then be $p_t=0.6$ and $p_c=0.38$, and their difference would be $0.6-0.38=0.22$, or 22%. The SE for the difference would be:

$$SE_{diff}=\sqrt{\frac{0.6\times0.4}{60}+\frac{0.38+0.62}{60}}=0.089$$

Then, the 95% CI would be $0.22-(1.96\times0.089)$ to $0.22+(1.96\times0.089)=0.05$ to 0.39. This means that although this study found a 22% improvement following treatment, the true response percentage is likely to be between 5% and 39%. In 95% of a large number of such trials conducted, the calculated CIs for the difference would include the true treatment response.

The Efficacy of Nebulized Metaproterenol in Wheezing Infants and Young Children

Anthony J. Alario, MD; William J. Lewander, MD; Penelope Dennehy, MD; Ronald Seifer, PhD; Anthony L. Mansell, MD

• The benefit of β-adrenergic agonists in the treatment of acutely wheezing infants and young children has not been well documented in the outpatient setting. To determine the efficacy of nebulized metaproterenol sulfate, 74 children aged 36 months or younger with acute wheezing participated in a double-masked, randomized, placebo-controlled clinical trial. Children received nebulized metaproterenol, either as an initial treatment or after a control treatment with normal saline solution. At baseline and 20 minutes after each treatment, an assessment was made that included measurements of heart rate, respiratory rate, oxygen saturation, and clinical variables related to respiratory compromise with the use of a standardized respiratory distress index (RDI). Children who received saline solution as initial therapy had no significant differences from baseline in any of the assessment measures. After metaproterenol therapy, children demonstrated an increase in heart rate ([mean±SD] 147±14 beats per minute vs 153±16 beats per minute), a decrease in respirations (50/min±5/min vs 45/min±7/min), improvement (lower scores) on the RDI (24±4 vs 15±2), and an increase in oxygen saturation (94.1%±2.7% vs 95.3%±3.0%). Patients aged 12 months or younger (n=37) benefited from metaproterenol treatment (improvement in respiratory rate and RDI) but not to the same degree as children aged 24 months or older (n=23) (improvement in respiratory rate, RDI, and oxygen saturation). Compared with assessments made before metaproterenol treatment, patients with respiratory syncytial virus infection (n=21) had improvement in respirations (52/min±7/min vs 45/min±6/min) and RDI scores (22±4 vs 14±3). Based on a priori criteria (reduction in a premedication respiratory rate of 20% *and* an RDI score of 50%), responders to metaproterenol therapy included 45% of the entire sample and, respectively, 40% of those aged 12 months or younger, 52% of those aged 24 months or older, and 48% of patients who tested positive for respiratory syncytial virus. Although there appears to be an age-dependent degree of response, metaproterenol is effective in relieving the respiratory distress of young acutely wheezing children, including those with documented respiratory syncytial virus bronchiolitis.

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Wheezing, especially wheezing associated with respiratory infection, is so common in the first 3 years of life (up to 11.4 cases per 100 children) that the use of β-adrenergic agents in this age group is widespread.[1-3] Although bronchodilators given by nebulization are safe and effective in older children,[4,5] studies have indicated that there is no substantial benefit of nebulized β-agonists for infants and toddlers.[6-12] Reasons that have been cited to explain the lack of response in infants to nebulized bronchodilators have included decreased bronchial reactivity, increased dynamic airway closure, immaturity of bronchiolar smooth muscle, and a relatively large degree of mucosal edema in infants as compared with that in older children.[2,13] On the other hand, there is recent evidence that infants and young children have the capacity to respond to bronchodilators. One partially masked, placebo-controlled study documented clinical improvement of young children in response to subcutaneous epinephrine,[13] and two case reports described dramatic responses in neonates given nebulized bronchodilators.[14,15] In addition, the airway responsiveness of wheezing infants challenged with histamine can be abolished by nebulized β-agonists, suggesting that functional adrenergic receptors are present in the airways of these young children.[16] The presence of β-receptors in human infants is further corroborated by findings from autoradiographic studies with labeled receptor-specific ligands that have documented the presence and distribution of β-receptors in young mammals.[17] We decided, therefore, that given the prevalence of episodic wheezing, a large randomized clinical trial was indicated to determine the efficacy of nebulized β-adrenergic medication in young wheezing children. We conducted a double-masked, randomized controlled trial to test the hypothesis that nebulized metaproterenol sulfate would produce objective improvement in acutely wheezing children aged younger than 36 months. In addition, we analyzed whether there were any

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differences in response to metaproterenol based on (1) the patient's age and (2) the presence of infection with respiratory syncytial virus (RSV).

METHODS

Subjects

The study was conducted during a 12-month period from April 1988 to April 1989. Children aged 1 to 36 months who presented to our outpatient facilities with acute episodes of wheezing or respiratory distress, present for less than 48 hours, were eligible to participate. Only episodes that were consistent with diagnoses of asthma, wheezing associated with respiratory illness, or bronchiolitis were included in the study.[13,18] Specific criteria for exclusion were as follows: (1) bronchodilator or steroid therapy within the previous 48 hours; (2) respiratory distress secondary to chronic cardiopulmonary problems; (3) a history of prematurity (<37 weeks' gestation); (4) respiratory difficulty in the neonatal period; (5) heart rate greater than or equal to 200 beats per minute or respirations greater than or equal to 100/min; and (6) requirement for immediate ventilatory support (eg, endotracheal tube placement). The study was approved by the hospital's committee on human subjects research, the details were explained to the families, and written informed consent was obtained. Before randomization of the subjects, we interviewed their parents or caretakers for demographic information that included family histories for asthma or atopy and histories suggesting exposure of the subjects to tobacco smoke for more than 3 hours each day.

Randomization and Treatment Schedule

As shown in Fig 1, the study was specifically designed to (1) provide timely intervention for young wheezing children with anxious parents and (2) maintain the masked nature of a randomized trial.

Children were randomized according to a balanced randomization schedule for every 10 patients with the use of a computer-generated random numbers table. Two vials of study solutions were prepared for each block of 10 patients. One contained a 5% solution of metabisulfite-free metaproterenol sulfate; the other contained normal saline solution without preservatives. As an initial treatment, the subjects were randomized to receive either 10 mg (0.2 mL of a 5% solution) of metaproterenol sulfate (n = 38) or 0.2 mL of normal saline solution (n = 36) as a control treatment. Each solution was diluted in 2 mL of 0.9% saline solution, administered by nebulization with the use of a compressed air apparatus without oxygen and given to the subject via face mask in a standard manner.[19] This dose of metaproterenol was chosen as it corresponded to doses of β-adrenergic agents used in previous research.[7-12] The actual amount of drug received, however, varied according to the size of the child and to the patient's tidal volume and minute ventilation.[5] Twenty to 25 minutes after the initial treatment, the subjects received the alternate agent. Thus, all participants were masked as to treatment assignment but still received medication in a timely manner. We hypothesized that there would be no beneficial effect from nebulized saline solution, nor did we anticipate a "washout" effect to occur in the group initially treated with metaproterenol followed by placebo. All treatments were administered by a respiratory therapist or nurse who was experienced in pediatric respiratory therapy, without the investigators present. Throughout the trial, the investigators, respiratory therapists, and nurses were unaware of which solution the patient was receiving; the solutions had the same odor and taste, when nebulized. If clinically indicated, a second treatment of metaproterenol was administered, and additional tests, medications, or hospitalization were ordered, as required.

Clinical Assessment

Before either treatment (baseline) and 20 minutes after each of the two treatments, a clinical assessment was performed by one of two investigators (A.J.A. and W.J.L.). The information obtained included heart rate, respiratory rate, and a standard recording of findings of respiratory distress previously shown to be important in the evaluation of children with lower respiratory tract disease, namely, the extent and degree of wheezing, chest wall retractions, flaring of the alae nasi, grunting, color, and responses to social overtures.[13,20-22]

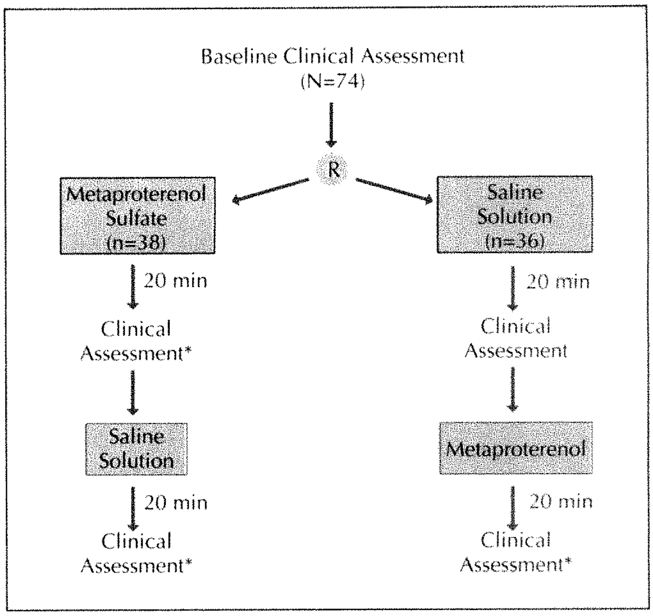

Fig 1.—*Outline of study design. Asterisk indicates the points in the study where clinical assessment data were pooled for analysis; R, point of randomization.*

Clinical impressions with regard to each of these latter six variables were coded on separate, continuous 12-cm lines that were calibrated to represent increasing degrees of severity (Fig 2). Thus, the investigator recorded the point on the scale that best represented the degree of clinical impairment associated with that variable. Treating an ordinal variable as a continuum was adopted as this allowed the investigators some latitude in scoring the subtleties of respiratory distress in young, wheezing children. For analysis, the distance along the line to the marked point was measured, and the total for all six variables was summed and termed the respiratory distress index (RDI) score. As an example, an infant with normal color, wheezing during expiration, and, occasionally, on inspiration, a moderate degree of intercostal and subcostal retractions, a moderate degree of flaring of the alae nasi, and who was somewhat irritable and not playful would attain an RDI score of 24.

Before initiating the study, two clinical investigators (A.J.A. and W.J.L.) carried out independent, simultaneous assessments in 20 acutely wheezing infants to standardize the RDI. Interobserver reliability for each variable was tested with the use of weighted percentage agreement and weighted κ.[23] For any variable on the RDI, there was no greater than 3 cm of discordance on the 12-cm line between investigators. The weighted percentage agreement ranged from 90% to 98%, and weighted κ ranged from .60 to .72, indicating good to excellent agreement.[24]

Arterial oxygen saturation was also measured at baseline and 15 to 20 minutes after each treatment with the use of a pulse Oximeter (Nellcor N-100, Nellcor Corp, Hayward, Calif) with an infant toe probe (Oxisensor I-20, Nellcor Corp). Measurements were made after the child had been quietly lying supine for 5 minutes. The recorded measurement was the single highest value noted during observation of the monitor for 30 seconds. For comparison, oxygen saturations were also obtained on a sample of 30 children of similar age who were attending a well-child clinic. The mean±SD oxygen saturation of these children was 97.7%±1.7%. The respiratory therapist or nurse recorded the patient's heart rate, blood pressure, and any side effects. A

Color:	Normal	Pale or Mottled Slightly	Circumoral Cyanosis With Crying	Circumoral Cyanosis at Rest	Generalized Cyanosis
Wheezing:	None	Terminal Expiration With STETH Only	Terminal Expiration +/– Early Inspiration With STETH	Entire Expiration+ Inspiration With STETH	Audible Expiration or Inspiration or Minimal Air Entry
Accessory Muscle Use:	None	Minimal IC or SC (+/–)	Moderate IC/SC (++)	Marked IC/SC or Supraclavicular (+++)	Extreme IC/SC or Supraclavicular, Palpable Contraction of Abdominal Muscles, Elevation of Clavicle (++++)
Flaring:	None	Mild, Infrequent (+/–)	Moderate, Intermittent, or Persistent (++)	Marked, Persistent (+++)	Severe, Persistent (++++)
Grunting:	None	Mild, Infrequent (+/–)	Moderate, Intermittent, or Persistent (++)	Marked, Persistent (+++)	Severe, Persistent (++++)
Distressfulness:	Content	Mildly Irritable When Touched, OCC Cry, Resists Then Accepts Bottle/Pacifier	Moderately Irritable, Intermittent Crying, Resists Comforting	Extremely Irritable, Crying Through Evaluation	Flaccid, Poorly Responsive, Moaning, or Weak Cry

Fig 2.—*Respiratory distress index: six variables, each scored on 12-cm line. STETH indicates stethoscope; plus/minus, one plus, two pluses, three pluses, and four pluses, refers to the severity of a particular respiratory variable; IC, intercostal; SC, subcostal; and OCC, occasional.*

nasopharyngeal aspirate was obtained by means of a sealed suction devise (De Lee Trap, Sherwood Medical, St Louis, Mo) before randomization, and the collected material was stored in phosphate buffer solution at −20°C for subsequent determination of RSV. The detection of RSV was performed with the use of an enzyme-linked immunosorbent assay (Ortho RSV Antigen Elisa Test [sensitivity, 91%; specificity, 88%], Ortho Diagnostic Systems Inc, Raritan, NJ).[25]

Statistical Analysis

Categoric variables (ie, demographic data) were analyzed with nonparametric statistics (eg, χ^2 test). Dimensional variables that were not normally distributed were analyzed by nonparametric tests (eg, Wilcoxon Rank-Sum test or Mann-Whitney *U* test), and those with normal distribution were analyzed by either the paired or unpaired *t* test (two tailed). Means and SDs were determined for heart rate, respiratory rate, the RDI score, and oxygen saturation. Further analyses were performed based on the patient age and RSV status. Post hoc analyses that corrected for type I errors when multiple comparisons were performed were applied to compare baseline vs treatment differences within subject groups and differences in the degree of response to treatment between subject groups.

In addition, to describe the sample's response to treatment in a clinically relevant manner, criteria that were developed before enrollment were used to identify responders. These criteria were derived in part during the pilot phase of the study and in part from previously published work.[13,20-22] A clinical responder was defined as a patient who had a reduction in *both* the respiratory rate, by at least 20%, *and* RDI score, by at least 50%, compared with premedication values when assessed 20 minutes after treatment. Expecting that 10% of patients who were treated with placebo might meet criteria for response as opposed to 50% of patients treated with metaproterenol, a sample of 36 patients in each arm would provide a power of 0.95 with an α of .05.

Sample Characteristics

Seventy-four patients were enrolled in the study, with two families refusing to participate. The mean age of the patients was 16.1 months, with a median age of 12 months. Fifty percent of the patients were aged 12 months or younger, 19% were aged between 13 and 23 months, and 31% were aged 24 months or older. Sixty-eight percent were male, 37% were white, 32% were black, and 31% were Hispanic. Sixty-five percent had a positive family history of asthma or atopy, and 64% of the sample had family members or caretakers who were household smokers. Seventy percent of patients were experiencing their first episode of wheezing; all but four of the 37 infants aged younger than 12 months were wheezing for the first time. There were no statistically significant differences between the group initially treated with saline solution (n = 36) and the group treated with metaproterenol (n = 38) with regard to age, gender, race, family history of asthma or atopy, the proportion of smokers in the household, weight, and initial temperature, or in the clinical assessment measures of heart rate, respiratory rate, RDI score, or oxygen saturation (Table).

RESULTS

Compared with the patients who received saline solution (n = 36) as an initial control treatment, patients who were treated with metaproterenol (n = 38) had significant improvement in respirations (51/min±5/min vs 44/min ±6/min, $P \leq .05$) and in the RDI score (23±3 vs 16±4, $P \leq .01$) at the first assessment, 20 minutes after initial treatment. No significant differences were noted in heart rate or oxygen saturation.

When compared with baseline, patients who initially received saline solution had no statistically significant differences in any of the clinical assessment variables. The data from both groups were therefore combined for comparison of clinical assessment measures immediately before and after metaproterenol treatment (Fig 1). Following treatment with metaproterenol, patients (N = 74) demonstrated significant improvement with a decrease in respirations (50/min±5/min vs 45/min±7/min, $P \leq .001$), improvement in the RDI score (24±4 vs 15±2, $P \leq .001$), and an increase in oxygen saturation (94.1%±2.7% vs 95.3%±3.0%, $P \leq .028$). There was also a significant increase in heart rate (147±14 beats per minute vs 153±16 beats per minute, $P \leq .002$) (Fig 3).

The patients who received metaproterenol initially and who were therefore reevaluated 50 minutes later demonstrated further improvement in respirations (44/min± 6/min vs 38/min±6/min, $P \leq .01$) and in the RDI score (16±4 vs 12±3, $P \leq .05$). Heart rate (150±16 beats per minute vs 148±18 beats per minute) and oxygen saturation (95.1%±2.6% vs 94.5%±3.5%) did not significantly change (Fig 4).

The data were then analyzed to determine whether response was affected by age or RSV status.

To maximize the effect of age and determine whether younger infants responded as well to metaproterenol treatment as the older cohort, the sample was divided into two groups: (1) children aged 12 months or younger and

Demographic and Clinical Characteristics of Patients at Baseline*

Characteristic	Treatment Order† Saline Solution/ Metaproterenol Sulfate (n=36)	Metaproterenol/ Saline Solution (n=38)	*P*
Age (median), mo	15±10 (11)	18±11 (14)	.27 (. . .)
Gender, % M	68	69	.69
Race, % W	38	36	.56
Positive family history for asthma/atopy, %	57	70	.23
Household smokers, %	66	60	.43
Weight, kg	10.1±3.1	11.3±3.4	.11
Temperature, °C	38.0±1.2	37.5±1.1	.14
Heart rate, beats/min	148±14	147±15	.76
Respirations/min	50±6	49±5	.81
RDI score	24±4	26±4	.37
Oxygen saturation, %	94.1±3.4	94.2±2.2	.94

*Data for indicated characteristics are given as means±SDs. RDI indicates Respiratory Distress Index.
†Metaproterenol was given as part of treatment.

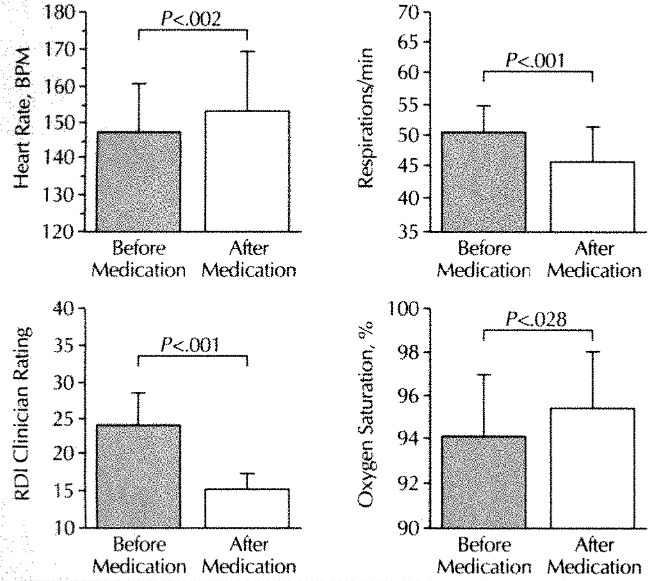

Fig 3.—*Comparison of clinical assessment measures before (shaded bars) and after (open bars) metaproterenol sulfate therapy for the entire sample (N=74). Values are expressed as means±SDs. BPM indicates beats per minute; RDI, respiratory distress index.*

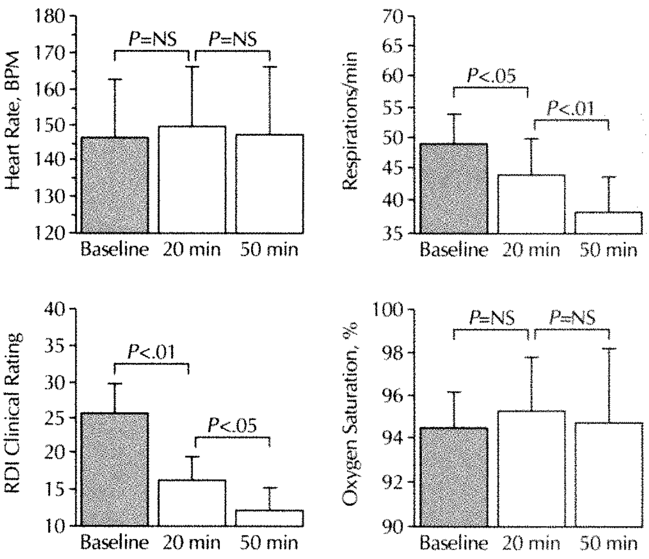

Fig 4.—*Comparison of clinical assessment measures at baseline (shaded bars) and 20 and 50 minutes after (open bars) medication in patients who received metaproterenol sulfate as an initial treatment (n=38). Values are expressed as means±SDs. BPM indicates beats per minute; NS, not significant; and RDI, respiratory distress index.*

(2) those aged 24 months or older. There were no differences in sociodemographic variables between the two age categories. The younger children had significantly higher premedication heart rates (152±12 beats per minute vs 139±11 beats per minute, $P \leq .01$), but baseline respiratory rates, RDI scores, and oxygen saturations did not differ. Following medication, only the older children demonstrated a significant increase in heart rate, but both groups had a significant decrease in respiratory rate ($P \leq .05$ for patients aged 12 months or younger; $P \leq .01$ for patients aged 24 months or older). The extent of the decrease in the respiratory rate of the older children was significantly greater than that observed in younger patients ($P \leq .05$). In both age groups, respiratory distress, as measured by the RDI, significantly improved after metaproterenol treatment ($P \leq .05$ for patients aged 12 months or younger; $P \leq .01$ for patients aged 24 months or older). Again, older children had a significantly greater degree of improvement compared with that in younger infants ($P \leq .01$). Oxygen saturation changed significantly only in the older group ($P \leq .05$) (Fig 5).

Sixty-two (84%) of 74 patients had nasopharyngeal specimens obtained to determine whether wheezing was associated with RSV infection, and 21 samples (34%) were positive. To control for any age-related differences in response to medication, the RSV-positive patients (mean age, 10.1 months) were matched to within 1 month of age with 21 RSV-negative patients. There were no significant differences between the two groups in sociodemographic variables, baseline heart rate, respiratory rate, RDI score,

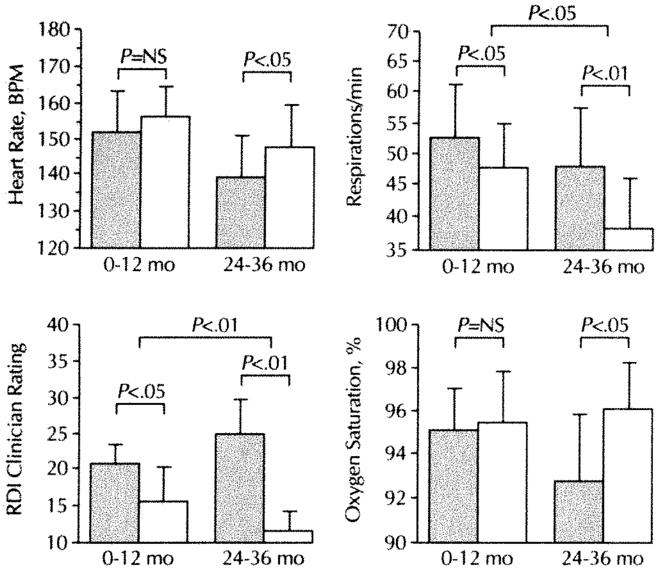

Fig 5.—*Comparison of clinical assessment measures before (shaded bars) and after (open bars) metaproterenol sulfate therapy in patients stratified by age (range, 0 to 12 months [n = 37]; range, 24 to 36 months [n = 23]). Values are expressed as means±SDs. BPM indicates beats per minute; NS, not significant; and RDI, respiratory distress index.*

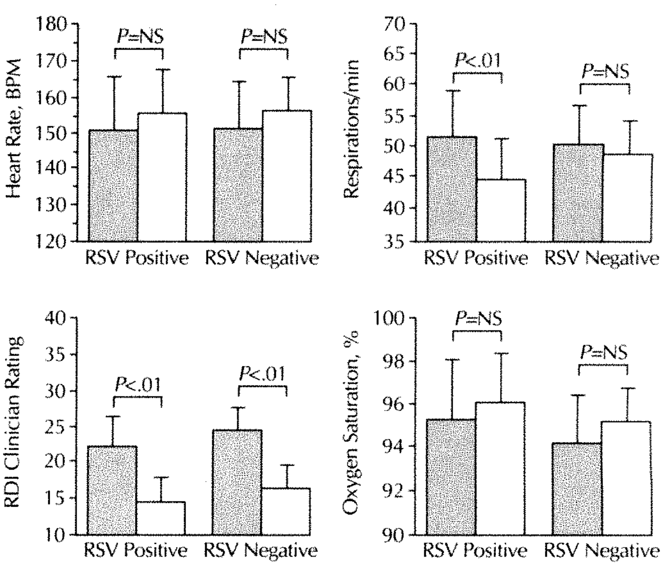

Fig 6.—*Comparison of clinical assessment measures before (shaded bars) and after (open bars) metaproterenol sulfate therapy in patients stratified by respiratory syncytial virus (RSV) status (RSV positive, n = 21; RSV negative, n = 21). Values are expressed as means±SDs. BPM indicates beats per minute; NS, not significant; and RDI, respiratory distress index.*

or oxygen saturation. There was also no significant clinical response to saline solution in either RSV-positive or RSV-negative children. Following metaproterenol treatment, only RSV-positive children demonstrated a significant decrease in respiratory rate ($P \leq .01$). Both groups, however, had improvement in RDI scores compared with premedication values ($P \leq .01$ for both). No differences in heart rates or oximetry measurements were noted. Neither group experienced a significantly greater degree of improvement over the other (Fig 6).

The proportion of patients defined as clinical responders, based on strict a priori criteria, was first determined based on initial treatment assignment. Only 3% (one patient) in the group that initially received saline solution (n = 36) met criteria as a responder in contrast to 53% (20/38, $P \leq .001$) of patients who were initially treated with metaproterenol. For the sample, as a whole, after treatment with metaproterenol, 45% (33/73) were responders. With respect to age, 40% (15/37) of those aged 12 months or younger and 52% (12/23) of those aged 24 months or older were responders. Forty-eight percent (10/21) of the RSV-positive patients were responders.

Nineteen patients (26%) were admitted (median age, 17 months); of these, seven (37%) were aged younger than 12 months. Those treated as outpatients received careful follow-up.

No significant untoward adverse effects, such as tremors, vomiting, or extreme irritability, were observed following treatment with nebulized metaproterenol. No patient experienced an increase in heart rate greater than 200 beats per minute or an increase in systolic blood pressure more than 20 mm Hg above baseline. One patient had a brief period of facial flushing.

COMMENT

This double-masked, placebo-controlled trial has demonstrated that treatment with nebulized metaproterenol is effective in relieving the respiratory distress of young infants and children aged younger than 36 months with acute wheezing. After treatment with nebulized metaproterenol, the children in the study sample as a whole had significant improvement in subjective and objective measures of respiratory distress compared with assessments before medication. In addition, the group that received metaproterenol initially had a continued medication effect (manifested by improvement in respiratory rate and the RDI score) that was documented by measurements made 50 minutes after metaproterenol was given. The duration of this degree of improvement is not addressed by this study. The implication, however, is that the continued improvement, noted in older patients, may also occur for some time in this young age group.[26]

As was expected, heart rates increased with metaproterenol therapy because of adrenergic stimulation of β_1-receptors. On further analysis, a statistically significant ($P < .05$) increase in heart rate was seen only in older patients. The reason for the lack of significant rise in the younger patients may have been due to a small sample size or the lack of an effect from the medication. Significant improvement did occur, however, in respiratory rate and RDI scores in this young age group. Overall, no clinically worrisome persistent elevation in heart rate was seen, and in fact, heart rates declined over time in patients who initially received metaproterenol, perhaps as a result of improvement of respiratory distress.

Although there was a statistically significant increase in oxygen saturation after metaproterenol therapy, the mean oxygen saturation of the study patients remained significantly below that of an age-matched sample from a well-child clinic (95.3%±3.0% vs 97.7%±1.7%, respectively; $P \leq .01$). When the data on oxygen saturation were examined for each patient, we noted that 12% of the sample had a decrease of at least 4% in oxygen saturation after metaproterenol therapy despite having improvement in respiratory rates and RDI scores. This discrepancy may be explained by a drug-mediated dilatation of pulmonary vessels supplying areas of the lung that remain poorly ventilated, leading to an inequality in ventilation and perfusion.[27,28] Alternatively, the period of observation may not have been long enough to identify significant improvement in oxygen saturation. Because of our study design, we did not administer treatments with oxygen, but our data indicated that young children with acute wheezing should be given oxygen, especially in light of hypoxemia and the potential for desaturation.

This study has shown that although young infants respond to β-adrenergic medication, there appears to be an age-dependent degree of response to bronchodilators.[9,10,13] Children aged older than 24 months improved to a significantly greater degree than those aged younger than 12 months. Whether there would be further improvement in the young infants after additional doses of metaproterenol is difficult to answer because of the study design. In one study, clinical improvement following epinephrine occurred in almost two thirds of wheezing children aged younger than 1 year, and the response to one epinephrine injection was not a reliable predictor of the final response to epinephrine.[13] Recently, Schuh et al[29] suggested that infants aged younger than 6 months who were given two doses of nebulized albuterol appeared to respond as well as older children, although their sample size was small.

As there is, at present, a controversy surrounding the efficacy[30-32] and potential hazards[33,34] of ribavirin in the treatment of infants with RSV bronchiolitis, we thought it important to evaluate the clinical response of these patients to standard bronchodilator therapy. It is often difficult on the basis of clinical information alone to differentiate the infant with RSV infection from one with "early asthma."[2,13] However, based on our data, wheezing patients with documented RSV infection respond equally as well to nebulized metaproterenol as age-matched children without RSV infection. The use of metaproterenol during the early stages of bronchiolitis may provide relief of respiratory distress and avoid the need for ribavirin therapy in many patients. We did not document whether less common infectious triggers of bronchospasm (eg, parainfluenza or adenovirus) were present in the RSV-negative patients. However, it is probable that young children with these infections would respond to metaproterenol in a similar manner to the patients with RSV infection.[29]

Considerable controversy exists with regard to the effectiveness of β-adrenergic agonists in the treatment of the wheezing infant and toddler. Several previous studies have reported the benefits of such therapy, but these studies suffered from small sample sizes, and the investigators often were not completely blinded.[13-15] The majority of reports indicate that there is little role for nebulized bronchodilators in this age group. Significant differences in study design may account for these discrepancies. In general, previous studies involved selected patients who were either hospitalized or studied in clinical research facilities.[6-12] We utilized an unselected population of outpatients who were experiencing acute respiratory distress. It is likely that the children in the former studies had a longer duration of symptoms and more progressive lower airway disease. Residual edema, inflammatory exudate, and epithelial necrosis with subsequent mucous plugging of small-caliber bronchioles may have rendered these infants less susceptible to inhalation therapy. Furthermore, the majority of these studies were unblinded, and sample sizes were inevitably small as the major outcome of interest, ie, pulmonary function, as measured by small-airway resistance, often requires cumbersome apparatus and sedation of the infants.[6-10] The validity of these measures of airway resistance by plethysmography and thoracic gas volume in wheezing infants has recently been challenged.[35] In addition, the lack of change in the measurement of pulmonary resistance following bronchodilators may have been masked by a reduction in functional residual capacity and residual gas volume associated with improvement in clinical status without any fall in resistance.[6] This mechanism has been postulated as an explanation for the inability to document a reduction in airway resistance, measured indirectly by means of forced vital capacity, despite clinical improvement in adults following bronchodilator therapy.[36] We were interested in clinically relevant and reproducible measures of respiratory distress and, therefore, were able to select a large sample size and conduct the study without disruption of routine short-term care practice.

Previous investigators have documented the safety of β-adrenergic agents in older children. In a study by Marks,[37] children aged between 1½ and 6 years received oral metaproterenol without any adverse reactions, and two recent studies that monitored the cardiovascular effects in children (age range, 2 to 14 years) who were treated as outpatients with either albuterol aerosol or syrup found no significant alterations in blood pressure or cardiac rhythm.[38,39] We found no clinically significant side effects from nebulized metaproterenol in this young population in the short-term care setting.

This study has shown that nebulized metaproterenol can be safely and effectively used in the treatment of acutely wheezing infants and toddlers. Although the clinical response appears most marked in patients aged older than 24 months, younger infants appear to benefit as well. In addition, nebulized metaproterenol and other β_2-agonists may be particularly useful in relieving respiratory distress in patients with the early symptoms of RSV bronchiolitis. Whether multiple doses of nebulized bronchodilators alone or in combination with other agents (eg, steroids), or whether newer forms of therapy, such as ipratropium bromide, have a significant clinical role in the young infant and toddler who wheeze will require further investigation.

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Prescribe

℞ **Pedia-Profen®**

Ibuprofen Suspension

100 mg/5 ml

Provides 6 to 8 hours of fever relief[1]

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Please see brief summary of Prescribing Information on the next page.

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Reference : 1. Walson PD et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17 information in **Pedia-Profen** labeling.

INDICATIONS AND USAGE: Pedia-Profen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: Pedia-Profen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **Pedia-Profen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Pedia-Profen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **Pedia-Profen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **Pedia-Profen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **Pedia-Profen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Meaningful (3 times the upper limit of normal), elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with **Pedia-Profen**. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), **Pedia-Profen** should be discontinued.

Safety and efficacy of **Pedia-Profen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats Administration of **Pedia-Profen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5 °F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: Pedia-Profen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)	NDC 0045-0469-04
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SHAKE WELL BEFORE USING. Store at room temperature.

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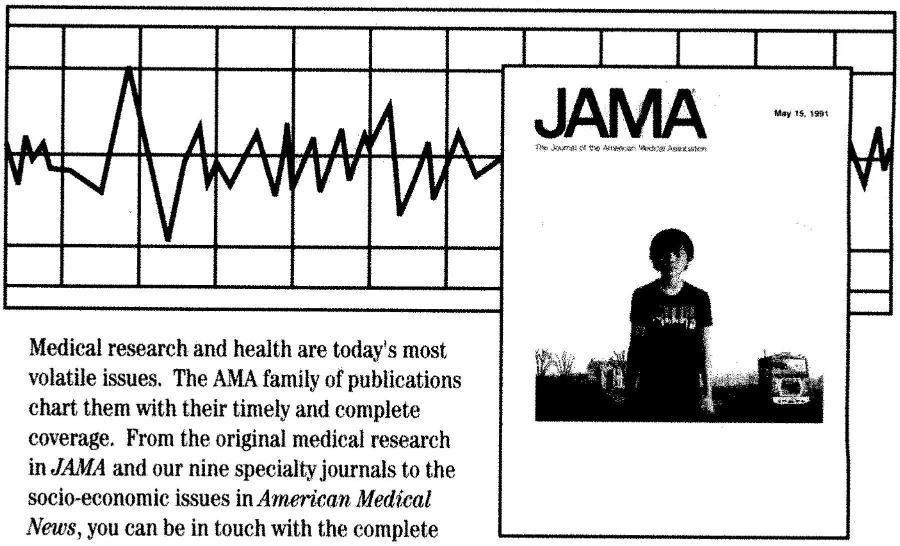
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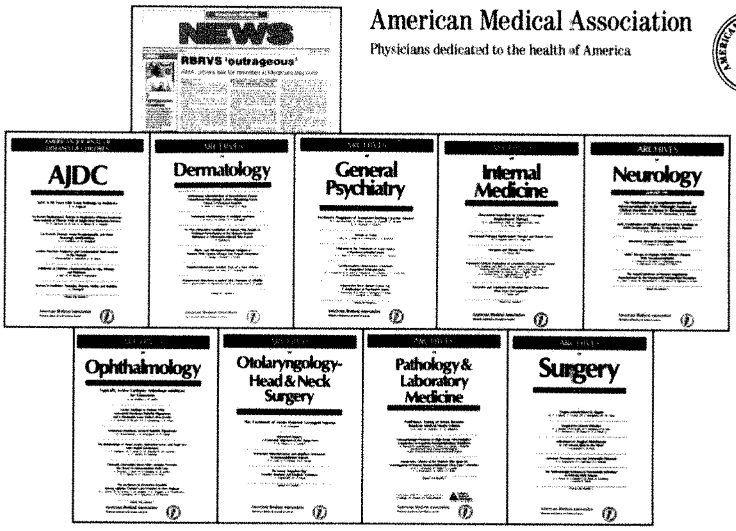

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2WEEX

SPECIAL FEATURE

Radiological Case of the Month

J. Lewis Gregory, MD; Darrell M. Wilson, MD; Bruce Parker, MD (Contributors);
Beverly P. Wood, MD (Section Editor)

A 9-year-old girl was in good health until presenting at a local emergency room with nausea, vomiting, constipation, and vague abdominal pain. A large abdominal mass was noted on physical examination, and an abdominal computed tomographic scan revealed a large intraperitoneal, multiloculated mass. She was taken to the operating room, where torsion of an enlarged left ovary was discovered and the intraperitoneal mass removed. On gross inspection, the ovary appeared polycystic, measured 14 × 11.5 × 7.5 cm, and weighed 570 g. The other ovary was also noted to be polycystic but was smaller. After surgery, she was noted to be short and to have early breast development. She was referred for endocrine evaluation. Before a workup could be performed, however, her abdominal pain recurred, and she was readmitted to the hospital.

Her medical history was significant only for birth by emergency cesarean section owing to fetal bradycardia secondary to a tight nuchal cord at 37 weeks' gestation. She had not received medical follow-up since her preschool checkup at age 5 years.

On admission she was in mild distress because of abdominal pain. Her height was 108 cm (4.2 SDs below the mean for her age), and her weight, 27.6 kg (in the 50th percentile for her age). On physical examination, she was noted to have all deciduous teeth and a normal thyroid. Breast development was Tanner II to III without galactorrhea. Results of genitourinary examination indicated Tanner I development. No axillary hair was present. She had a large, firm, abdominal mass 15 cm in diameter.

An abdominal ultrasound study revealed a 15-cm multicystic mass originating from the right ovary (Fig 1). Chest and abdominal roentgenograms were unremarkable except for the presence of the large intra-abdominal mass. Roentgenograms of the hands showed a bone age of 3 years (6 SDs less than the mean for her age).

Figures 2 and 3 show the decreased size of the ovary after treatment.

Accepted for publication June 18, 1990.

Contributed from the Departments of Pediatrics (Drs Gregory and Wilson) and Radiology (Dr Parker), Stanford (Calif) University Hospital.

Reprint requests to Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

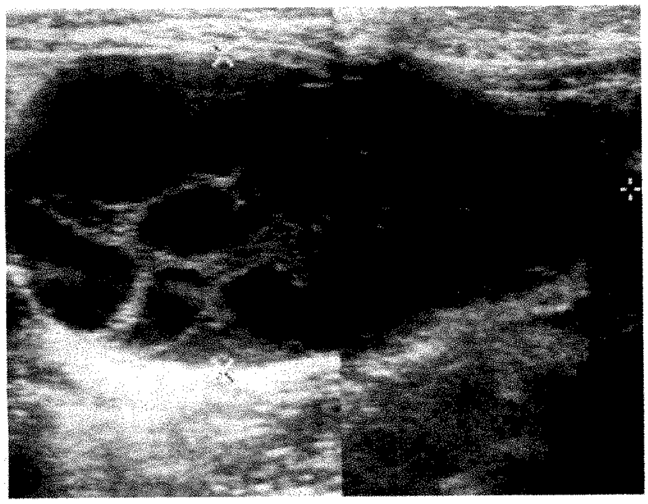

Figure 1.

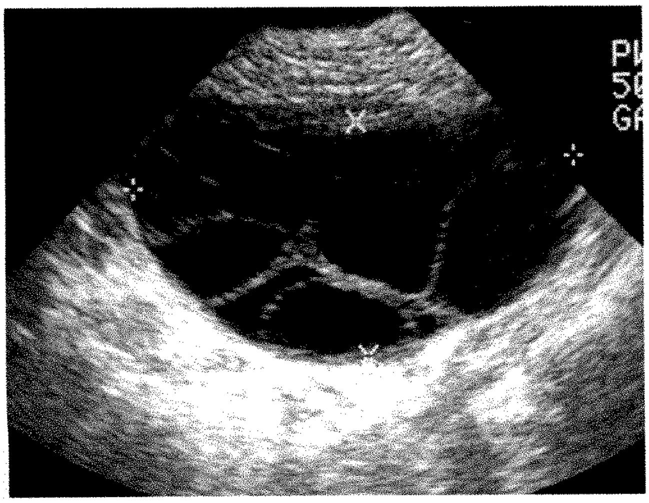

Figure 2.

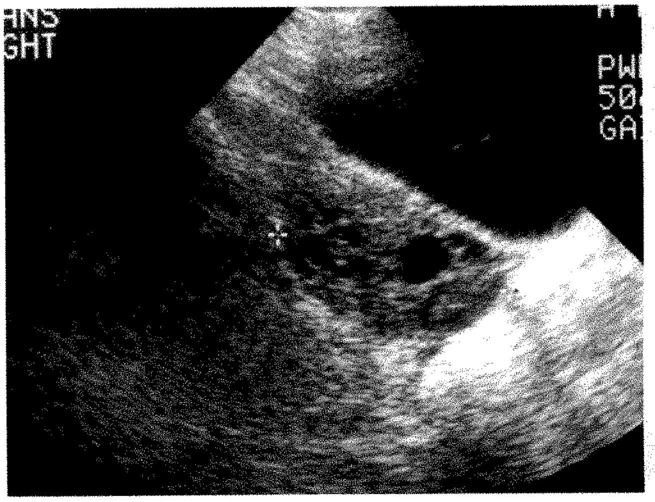

Figure 3.

Denouement and Discussion

The Overlap Syndrome: An Unusual Presentation

Fig 1.—*Longitudinal pelvic sonogram showing a multicystic, septated right ovary measuring 15.3 × 7.6 cm.*

Fig 2.—*Sonogram 3 weeks later when ovary measured 10.6 × 5.6 cm.*

Fig 3.—*Sonogram 10 weeks later; the ovary was 5.2 cm long. The cysts had shrunk significantly.*

As results of thyroid studies revealed, this patient was suffering from severe, longstanding hypothyroidism. Her level of serum thyroid-stimulating hormone was 2485 mU/L (normal range, 0.4 to 7.0 mU/L), and her thyroxine level was 5.15 nmol/L (normal range, 56.6 to 148.1 nmol/L). Treatment was begun with 50 μg of levothyroxine sodium administered daily, and, 1 week later, her level of serum thyroid-stimulating hormone was 1340 mU/L, and her thyroxine level was 82.4 nmol/L. Symptoms resolved and the ovary became smaller (Figs 2 through 4) without surgical intervention. Six months later, she had grown almost 5 cm and lost 3.7 kg. She continued taking 100 μg of levothyroxine sodium daily, and results of thyroid studies remained normal.

The overlap syndrome is a well-described, poorly understood phenomenon of precocious puberty occurring with juvenile hypothyroidism. In 1905, Kendle[1] first described a case of precocious puberty in a female cretin who had been treated with sheep thyroid extract for 2 years. Administration of the extract was discontinued at age 3 years, and by age 5 years she had breast development and had begun menses. Delayed pubertal maturation is common in association with hypothyroidism. Precocious puberty was initially thought to be a rare phenomenon. However, Barnes et al[2] described a large series of patients with hypothyroidism in which 31 (57%) of 54 patients showed advanced isosexual maturation relative to bone age. Most of these patients exhibited longstanding and severe hypothyroidism. From 1955 to 1965, several case reports in the literature described precocious puberty and enlarged multicystic ovaries in association with juvenile hypothyroidism.[3-7] Van Wyk and Grumbach described three patients with juvenile hypothyroidism and precocious puberty, one of whom had multicystic ovaries. They postulated that excessive secretion of pituitary hormones, thyroid-stimulating hormone, prolactin, and gonadotropins occurred because of deficient production of a single hormone and the subsequent overproduction of a hypothalamic factor, in this case, thyrotropin-releasing factor. In this setting, the high concentrations of thyrotropin-releasing factor appear to cross over and stimulate the secretion of other pituitary glycoproteins, such as the gonadotropins, in addition to thyroid-stimulating hormone. Thus, the phenomenon has been referred to as the overlap syndrome.

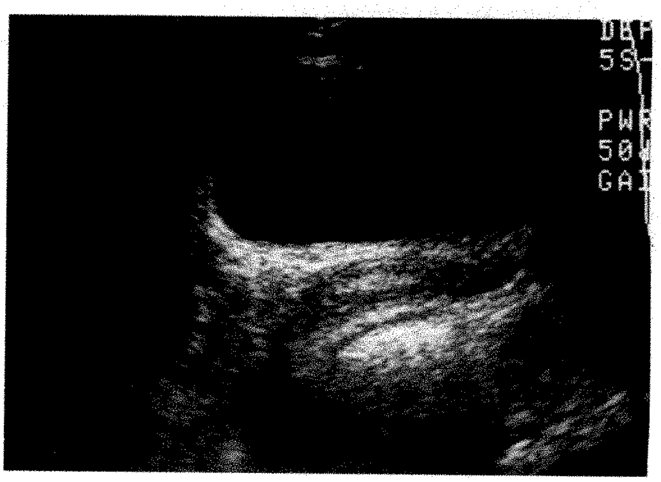

Fig 4.—*Transverse sonogram of the pelvis 9 months after initial examination demonstrates a normal prepubertal uterus. The ovary could not be identified.*

Since then, small series reported by Lindsay et al[8] and Riddlesberger et al[9] have described multicystic ovaries in association with precocious puberty in girls with juvenile hypothyroidism. Lindsay et al described a series involving 12 girls with severe and longstanding primary hypothyroidism, nine of whom were shown to have multicystic ovaries with pelvic ultrasound studies. Using pelvic ultrasonography, these investigators more accurately determined the prevalence of multicystic ovaries in primary hypothyroidism.

Torsion of the ovary is a rare but serious complication of multicystic ovaries. Hypothyroidism is an unusual but treatable cause of multicystic ovaries in girls. In this case, unnecessary surgical resection of the remaining ovary was averted with diagnosis and treatment of her underlying endocrinopathy.

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SPECIAL FEATURE

Radiological Case of the Month

Paul K. L. Lam, MBBS, MRCP, Yu-Lung Lau, MD, MRCP (Contributors);
Beverly P. Wood, MD (Section Editor)

A full-term, spontaneously delivered female newborn was assessed for existence of a systolic heart murmur. A chest roentgenogram at age 4 days was normal. At age 2 weeks, she became more tachypneic and fed more slowly. Examination showed an afebrile, well-nourished infant with a respiratory rate of 90 breaths per minute. There were subcostal retractions and slight respiratory crepitation on auscultation. A heart murmur was considered insignificant. The liver was massively enlarged, extending 6 to 7 cm below the costal margin at the midclavicular line, with a smooth border and a firm consistency. Another chest roentgenogram (Fig 1) showed coarse mottling and nodular opacities in both lungs. Sepsis workup, including a lumbar puncture, was performed. Results of biochemical and microscopic evaluation of cerebrospinal fluid were normal. The infant began receiving intravenous cefotaxime, cloxacillin, and amikacin. One day later, the left big toe of the infant became darkened, indicating the beginning of a gangrenous process.

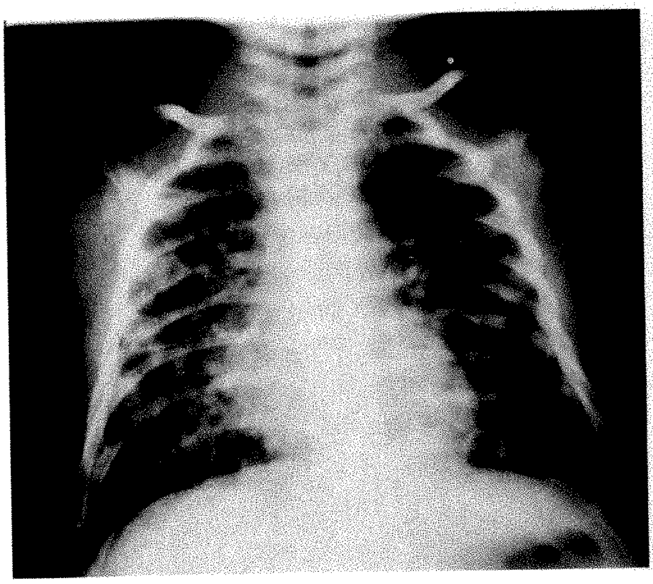

Figure 1.

From the Department of Paediatrics, University of Hong Kong, Queen Mary Hospital.
Reprint requests to the Department of Radiology, Box 81, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90054-0700 (Dr Wood).

Denouement and Discussion

Neonatal Tuberculosis

Fig 1.—*Frontal chest roentgenogram shows diffuse nodular parenchymal disease.*

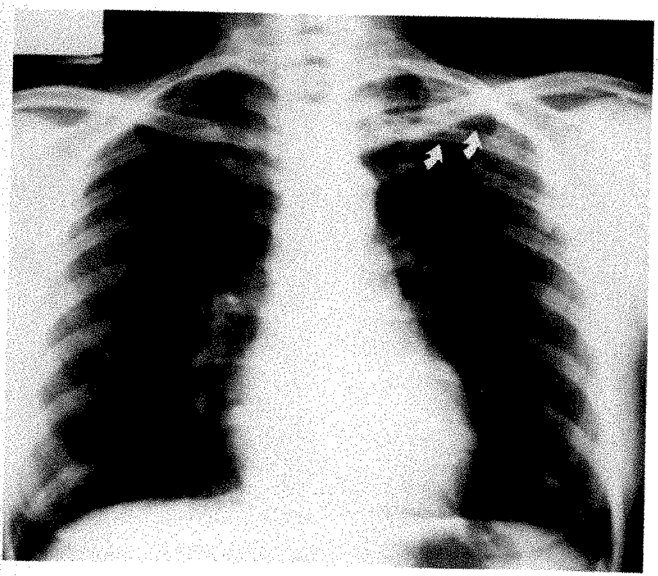

Fig 2.—*Frontal chest roentgenogram shows a patch of consolidation in the left apex. A central cavity is present (arrows).*

The patient's mother was an occupational therapist working in an outpatient clinic. She described a periodic cough for several weeks before delivery, with no fever or systemic illness. She was advised to undergo chest roentgenography, which showed a density and central cavity at the apex of the left lung (Fig 2) that were noted in retrospect. Gastric aspirate of the baby was analyzed microscopically to detect acid-fast bacilli, which were abundant. The patient immediately began receiving isoniazid, rifampicin, and amikacin, with gradual favorable response. Both the baby's and mother's sputum later yielded *Mycobacterium tuberculosis* on culture, and the mother was also enrolled in antituberculous therapy. The baby's cerebrospinal fluid, blood, and surface swabs were sterile. The gangrenous big toe gradually became demarcated, with sloughing of the distal one third of the toe and spontaneous granulation and healing of the stump. To our knowledge, gangrene of the extremities has not been reported in association with tuberculosis.[1-3] This baby had not undergone vascular catheterization or received any vasoactive agents incriminated as causes of gangrene. The nature of the gangrene is uncertain because no biopsy was performed. The father and other contacts of the mother were screened, and none had sources of infection.

This is not a case of congenital tuberculosis according to Beitzke's[4] diagnostic criteria. However, Hageman et al[5] stressed that the distinction between congenital and early neonatally acquired tuberculosis was primarily epidemiologic because the modes of presentation, treatment, and immediate prognosis were essentially the same. Our case of neonatal tuberculosis had features similar to the 24 cases of congenital tuberculosis described since the introduction of isoniazid[5]: (1) hepatomegaly and respiratory distress as presenting signs, (2) use of gastric aspirate to confirm the diagnosis, and (3) maternal disease often missed until the diagnosis was made in the neonate. Infant mortality related to this condition is still high (46% of cases) and results of skin tests are usually negative.[5] With prompt recognition and adequate treatment, the disease is curable.[6]

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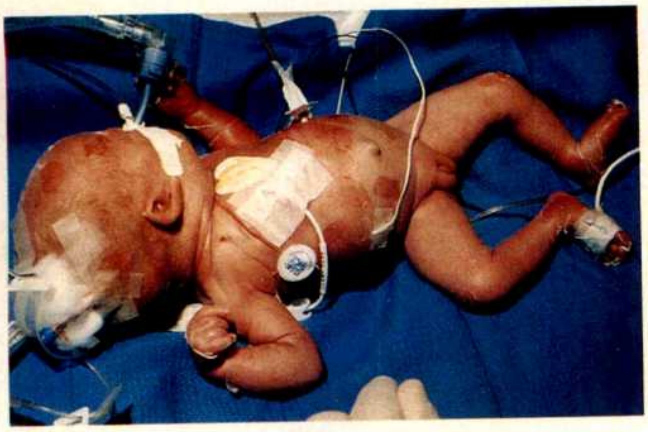
SPECIAL FEATURE

Picture of the Month

Oussama Itani, MD; Ruth Crump, MD; Francis Mimouni, MD (Contributors);
Walter W. Tunnessen, Jr, MD (Section Editor)

Figs 1 through 4.—*At age 3 weeks, this premature infant abruptly developed hypotension and large areas of denudation of the skin and required increased ventilatory assistance.*



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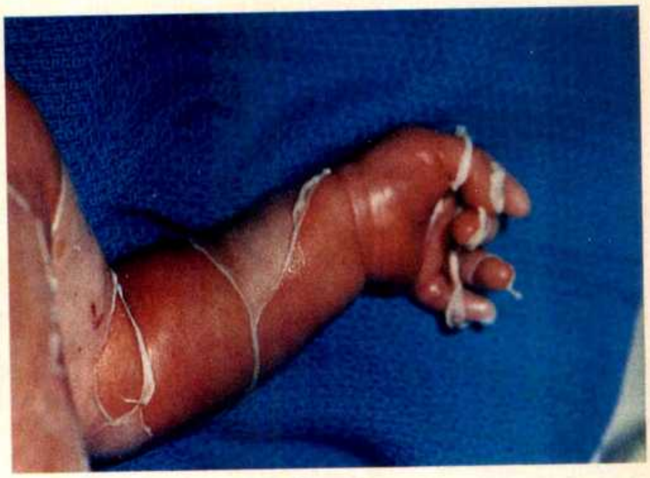

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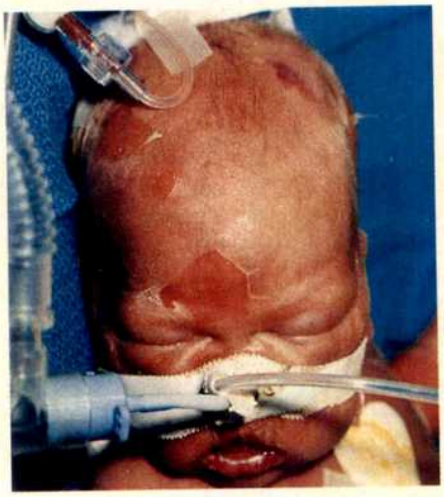

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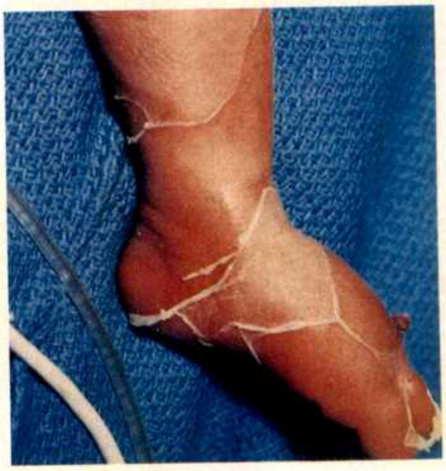

Figure 4.

Accepted for publication June 2, 1991.

Contributed from the Department of Pediatrics, Division of Neonatology, University of Cincinnati (Ohio) Medical Center.

Reprint requests to the Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Tunnessen).

Denouement and Discussion

Ritter's Disease (Neonatal Staphylococcal Scalded Skin Syndrome)

Figs 1 through 4.—*Large areas of skin denudation are evident, particularly on the hands and feet. Note the generalized background erythema of the skin.*

Historical Background

Baron Gotfried Ritter von Rittershain was the first to describe this dramatic exfoliative disease of newborns, having done so in 1878.[1] During a 10-year period, 297 cases occurred in the orphanage in Prague, Czechoslovakia, where he served as physician. He labeled the disorder dermatitis exfoliativa neonatorum, but was unsure of its cause. In 1956, Lyell[2] renewed attention to this striking disorder, which he described as resembling scalding. Not until 1970, however, did Melish and Glasgow[3] demonstrate in newborn mice that *Staphylococcus aureus*, particularly group 2 phage strains, types 71 and 55/71, were responsible for this condition. They postulated that the release of an exfoliative toxin by the staphylococci caused the widespread scaldlike presentation.

Clinical Manifestations

Skin lesions produced by exfoliative toxin-producing staphylococci vary from localized effects seen in bullous impetigo to a scarlet fever–like disorder, to the fully developed staphylococcal scalded skin syndrome with extensive skin separation. Ritter's disease is the name applied when neonates are affected by this disorder.

The appearance of erythema of the skin may be preceded by fever, malaise, and irritability, but often the erythema is abrupt in onset. It generally appears first on the head and neck and then spreads to the rest of the body, usually within 24 hours. The rash is accentuated in flexural creases. The skin is quite tender to the touch, and the affected infants are irritable and uncomfortable. Sheets of skin may peel away in response to minor trauma (Nikolsky's sign), creating moist, glistening surfaces that may cause significant fluid losses in infants. Generally, the denuded areas dry quickly, leaving a varnished-like surface. Spontaneous blisters also appear, but rapidly rupture. Within 24 to 48 hours, the surfaces appear dry. Desquamation begins within 3 to 5 days of onset, with complete clearing of the skin in 6 to 12 days.

The face may appear edematous, with a characteristic crusting around the mouth and eyes, especially in older infants and children. The crusting, consisting of radial spokes of thick desquamating skin, may not appear until the second day of illness. Initially, the erythematous generalized rash may have a sandpaperlike texture, suggesting the diagnosis of scarlet fever. The appearance of areas of denudation, the intense skin tenderness, the lack of a "strawberry" tongue, and the sunburstlike perioral and periorbital crusting should easily distinguish staphylococcal scalded skin syndrome from scarlet fever.

Laboratory Confirmation

The bullae and denuded skin surfaces are usually sterile. The staphylococci producing the exfoliative toxin can usually be cultured from the nares, conjunctivae, pharynx, or, less commonly, blood. Phage typing is not routinely available in hospital laboratories.

This syndrome was often equated with toxic epidermal necrolysis, which, clinically, is a much different disease that is usually caused by reactions to drugs or viral infections. In staphylococcal scalded skin syndrome, separation of the skin layers occurs in the epidermis, while in toxic epidermal necrolysis the separation is much deeper, occurring at the dermoepidermal junction.

Prognosis and Treatment

Although this disease can be devastating in neonates, older infants or children usually fare quite well, despite the denuded, erythematous, tender skin. Attention must be paid to adequate hydration, particularly in infants. Penicillinase-resistant antistaphylococcal antibiotics should be administered to prevent secondary septic complications. Neonates must be isolated, and nursery procedures carefully scrutinized for breaks in technique. Samples from nursery personnel may need to be cultured to detect staphylococcal carriers. Skin care consists of compresses applied to denuded areas and mild emollients to treat dryness of the skin.

Differential Diagnosis

In neonates, congenital epidermolysis bullosa may resemble Ritter's disease because of the areas of mechanically induced denudation. Epidermolysis bullosa is usually manifest at birth, while Ritter's disease never is. Epidermolysis bullosa also lacks the generalized erythema characteristic of Ritter's disease. Bullous impetigo is localized and also does not cause a generalized erythema. Toxic epidermal necrolysis is characterized by target lesions and severe mucosal involvement.

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Pathological Case of the Month

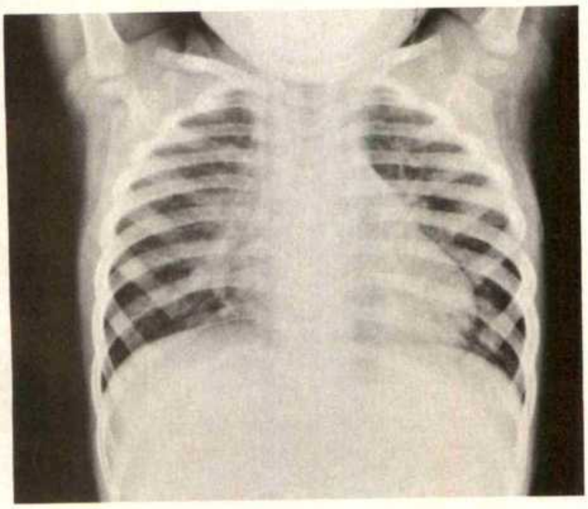
Mark R. Weatherly, MD; James M. Stark, MD, PhD; P. Syamasundar Rao, MD; Frederic Askin, MD (Contributors); *Enid Gilbert-Barness, MD* (Contributor and Section Editor)

A 15-month-old boy presented with tachypnea and rales on examination after a mild upper-respiratory tract infection. Pregnancy and delivery were normal. An intermittent nonproductive cough developed at approximately age 5 months that did not improve with bronchodilators. At age 12 months, intercostal retractions, crackles, and wheezes were noted. The retractions continued despite nebulized bronchodilators and oral corticosteroids. The family history was negative for cystic fibrosis, asthma, or cardiovascular disease. There was one smoker and one dog in the home, but no woodburning stove or fireplace.

Laboratory findings were as follows: sweat chloride, normal; arterial oxygen saturation, 96%; hemoglobin, 130 g/L; prothrombin time, 11.3 seconds; activated partial thromboplastin time, 25.0 seconds; and erythrocyte sedimentation rate (Wintrobe method), 4 mm/h. Titers of respiratory viruses in serum were nondiagnostic.

A chest roentgenogram (Fig 1) and angiogram (Fig 2) were obtained.

An electrocardiogram demonstrated possible right ventricular hypertrophy. An echo-Doppler study demonstrated normal anatomy and normal estimated pulmonary arterial pressure. An open-lung biopsy was performed (Figs 3 and 4).



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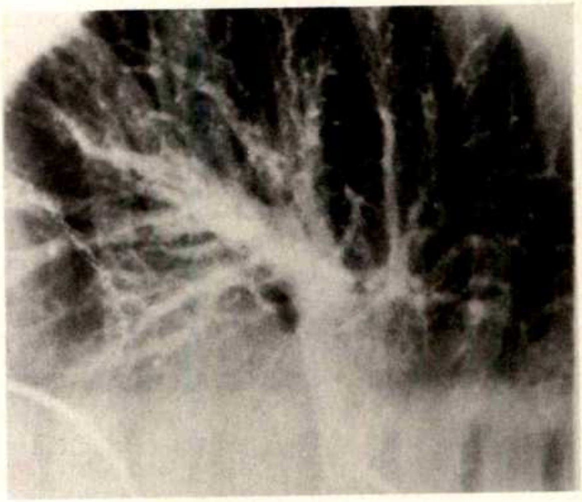

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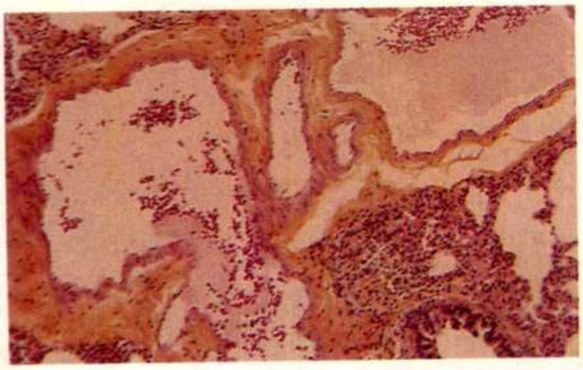

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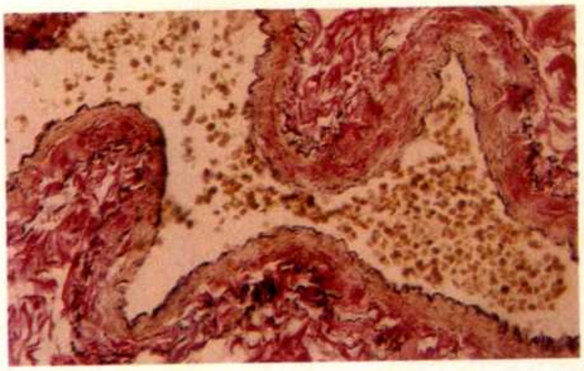

Figure 4.

Accepted for publication January 9, 1992.

From the Departments of Pediatrics and Pathology, University of Wisconsin Hospital and Clinics, Madison (Drs Weatherly, Stark, Rao, and Gilbert-Barness), and the Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Md (Dr Askin).

Reprint requests to Departments of Pathology and Pediatrics, University of Wisconsin, Center for Health Sciences, E5/326, 600 Highland Ave, Madison, WI 53792.

Diagnosis and Discussion

Pulmonary Angiodysplasia

Fig 1.—*A chest roentgenogram demonstrates the prominence of interstitial markings bilaterally, but more prominently in the right middle lobe.*

Fig 2.—*An angiogram demonstrates increased arborization of the pulmonary vasculature.*

Fig 3.—*Microscopic section of the lung showing peribronchiolar, thin-walled, dilated vascular spaces (hematoxylin-phloxine-saffron, original magnification ×100).*

Fig 4.—*Microscopic section of the lung showing dilated tortuous vascular space with disruption of the elastica (elastic van Gieson's stain, original magnification ×250).*

Microscopic sections of the lung biopsy specimen showed a striking proliferation of vascular spaces in the peribronchiolar zones, many of which were dilated, ectatic, and tortuous without thrombi (Fig 3). These vessels appeared to be principally venous channels, although arterial vessels were also present. Vessels showed disruption of the elastic tissue (Fig 4).

Angiodysplasia may occur as isolated or multiple arteriovenous fistulas or as a telangiectatic defect involving both venous and arterial channels. The lesion may be confined to the lung or may be a component of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease),[1] which accounts for one third to one half of the cases.[2-4] In a series of 350 cases described by Bosher et al,[5] 64% of patients had one arteriovenous fistula, most commonly in lower lobe. Most cases of angiodysplasia of the lung are unilateral, although bilateral involvement may occur. There is no sex predilection. Histologically, transitions between arterial and venous channels occur even within the same vessel. The vessels may be thick-walled or extremely thin-walled owing to loss of muscle and elastic tissue in the media. The intrapulmonary shunt may result in varying degrees of reduced oxygen saturation in the systemic circulation. The usual clinical findings are cyanosis and dyspnea with hypoxemia, polycythemia, increased risk of thrombosis/embolism, and neurologic symptoms.[1] The incidence of cerebral abscess is increased. Genetic implications are important if the lesion results from hereditary hemorrhagic telangiectasia, an autosomal-dominant trait.

The lung biopsy resulted in the diagnosis of pulmonary angiodysplasia, a more general term for pulmonary hemangiomatosis.[1,6] This disorder should be distinguished from capillary hemangiomatosis,[7] a possibly related but more invasive and destructive disorder. Pulmonary angiodysplasia is uniformly fatal when the patient is treated with conventional methods (eg, corticosteroids and cytotoxic drugs).[7,8] Five patients have been treated with interferon alfa-2a. One patient, after 3 years of therapy, had regression of the disease, and one patient with massive cutaneous hemangiomas died despite therapy.[9,10] Our patient was much younger than the patients described in the literature.

Our patient was treated with interferon alfa-2a at an initial dose of 3×10^6 U/m^2 per day administered subcutaneously. The protocol used was developed by White et al[10] for the management of angiomatous diseases. Three months after diagnosis, the patient required supplemental oxygen nocturnally. The dose of interferon was doubled, with subsequent stabilization of disease, based on clinical and angiographic data. Six months after this dose adjustment, he required less supplemental oxygen. He continued to receive daily injections of interferon alfa-2a and grew according to the growth curve for his age group and gender. However, he remains symptomatic, with tachypnea and intercostal retractions.

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The Editors welcome contributions to Pathological Case of the Month, Picture of the Month, *and* Radiological Case of the Month. *Those who wish to contribute should send their manuscripts to Dr Gilbert-Barness (*Pathological Case of the Month*), Center for Health Sciences, E5/326, University of Wisconsin Hospitals and Clinics, Madison, WI 53792; Dr Tunnessen (*Picture of the Month*), The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104; or Dr Wood (*Radiological Case of the Month*), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

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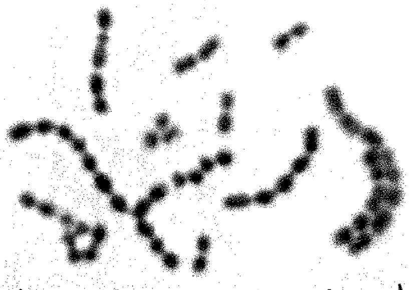

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* From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride supplementation: Revised dosage schedule. *Pediatrics* 1986; 77(5):758-761.

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POLY-VI-FLOR 0.5 mg with Iron	Drops	50 mL Bottle	0.5
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POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
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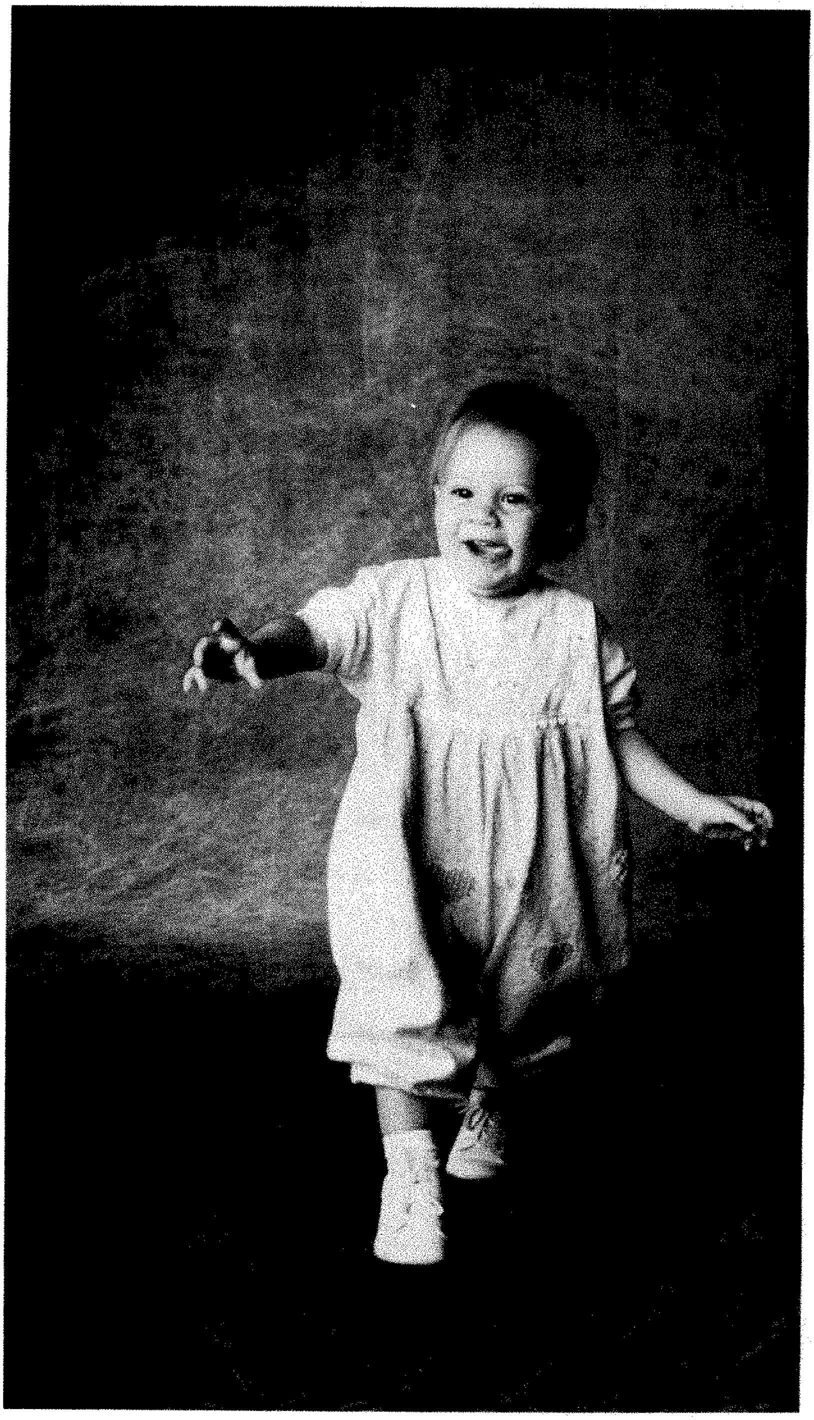

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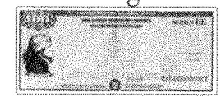

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CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risks of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension. Ibuprofen can inhibit platelet aggregation and prolong bleeding time.

CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions. Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 6 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence), heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculo-bullous eruptions; aseptic meningitis, fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coomb's positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (eg., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

* Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children). 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

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Assessment of Otoscopists' Accuracy Regarding Middle-Ear Effusion

Otoscopic Validation

Phillip H. Kaleida, MD, Sylvan E. Stool, MD

• Validation of otoscopic diagnostic accuracy is an important aspect of medical education and is necessary to substantiate clinical research observations. In addition, otoscopic accuracy is a prerequisite to optimal patient care. We describe an otoscopic validation program at the Children's Hospital of Pittsburgh (Pa) in which 27 physicians and three nurse practitioners participated from December 1980 to March 1990. The lowest acceptable limits for sensitivity and specificity regarding the diagnosis of middle-ear effusion were arbitrarily set at 80% and 70%, respectively. The 30 participating clinicians examined a total of 4147 ears. Mean sensitivity and mean specificity for the group as a whole were 87% and 74%, respectively. The chief benefit of the program was an improvement in diagnostic skills for some individuals. The chief limitation was the large amount of time required. We conclude that a formal validation program can document achievement of a reasonable standard of otoscopic diagnostic accuracy.

(*AJDC.* 1992;146:433-435)

Although accurate diagnosis of otitis media is important, recognition of the presence or absence of middle-ear effusion is often difficult, even for experienced otoscopists. In clinical settings, practitioners base treatment options (both medical and surgical) on otoscopic determinations. In educational settings, academicians must teach proper pneumatic otoscopic techniques and correct diagnoses to nurse practitioners, medical students, and house officers. In clinical investigations of otitis media, accurate diagnosis is essential because the presence of middle-ear effusion is often used as a primary outcome measure. For these reasons, documentation of otoscopic accuracy provides considerable advantages. Yet, to our knowledge, formal assessment of otoscopic diagnostic accuracy is performed infrequently. We report our experience at the Children's Hospital of Pittsburgh (Pa) with a program in which clinicians can "validate" their otoscopic accuracy regarding the detection of the presence or absence of middle-ear effusion.

SUBJECTS AND METHODS

Orientation and Feedback

Before the start of the validation procedure, each participant meets with one of the program directors (P.H.K.). The validation procedure is explained in detail and an instruction sheet is provided. In most cases, participants are required to examine a minimum of 100 ears. After examining each group of 50 ears, the trainee meets again with one of the program directors (P.H.K. or S.E.S.). During this meeting, progress to date is reviewed and, when possible, suggestions are made.

Validation Procedure

Children are examined in the Children's Hospital of Pittsburgh Same Day Surgery Unit where a system for incorporating the otoscopist into the patient flow has been formalized. These children, who have a history of recurrent or chronic otitis media, or both, have been scheduled independently of this program for elective myringotomy (with or without tympanostomy tube placement) under general anesthesia. The children range in age from infants to school-age and most do not have predisposing conditions. The otoscopists examine each child approximately 30

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC*

Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

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From the Division of Ambulatory Pediatrics, Department of Pediatrics (Dr Kaleida) and the Division of Pediatric Otolaryngology, Department of Otolaryngology (Dr Stool), University of Pittsburgh (Pa) School of Medicine, Children's Hospital of Pittsburgh (Pa).

Presented in part at the Sixteenth Annual Meeting of the Society for Ear, Nose, and Throat Advances in Children (SENTAC), New York, NY, December 4, 1988, and at the Fifth International Symposium on Recent Advances in Otitis Media, Ft Lauderdale, Fla, May 21, 1991.

Reprint requests to Children's Hospital of Pittsburgh, Department of Pediatrics, Ambulatory Division, 3705 Fifth Ave at DeSoto Street, Pittsburgh, PA 15213-2583 (Dr Kaleida).

minutes before myringotomy. Trainees are asked to use the same piece of equipment, a Welch Allyn model 20200 pneumatic otoscope (Welch Allyn, Skaneateles Falls, NY). Participants are told to attempt to examine the ears of all children (unless premedicated) scheduled for myringotomy during their assigned weekday morning session(s). Each otoscopist is instructed to determine, whenever possible, the presence or absence of middle-ear effusion in every ear examined.

A standard form is used to record the otoscopist's diagnoses. This form is affixed temporarily to the front of the medical record so that these diagnoses are obscured and only the section of the form to be completed by the surgeon is displayed. The determination of the presence or absence of middle-ear effusion during myringotomy is made with an operating microscope by an otolaryngologist who is unaware of the otoscopist's diagnoses. Specifically, the otoscopist undergoing validation cannot be the same individual diagnosing the presence or absence of middle-ear effusion at myringotomy. The otoscopists' diagnoses are compared later with the surgeons' recorded findings.

Determination of Validity

Validity is determined by demonstrating a high degree of correlation of otoscopic diagnoses with myringotomy findings. Sensitivity is defined as the percentage of ears with effusion at myringotomy, diagnosed correctly by the otoscopist. Specificity is defined as the percentage of ears without effusion at myringotomy, diagnosed correctly by the otoscopist. Based on earlier experience with master otoscopists, we arbitrarily set the lowest acceptable limits for sensitivity and specificity at 80% and 70%, respectively. On completion of the program, a summary letter and a certificate are sent to the otoscopist undergoing validation.

RESULTS

Study Population

Data are presented for participants who completed the validation program during the period from December 2, 1980, to March 5, 1990. Twenty-seven physicians and three pediatric nurse practitioners comprised this group. Eleven of the 15 otolaryngologists were fellows in pediatric otolaryngology. Seven of the 12 pediatricians were private practitioners who, like the pediatric nurse practitioners, expected to participate in otitis media research. Thus, most of the otoscopists had at least a moderate amount of preparticipation experience.

Number of Ears Examined

The Table shows the total and mean numbers of ears that participants were required to examine for validation, according to specialty. The entire group of 30 trainees performed 4147 ear examinations, or a mean of 138 ears per trainee. Overall, participants examined slightly more ears with effusion (55%) than ears without effusion, but many ears were without effusion at the time of surgery.

Time To Validation

The mean time to validation for the total group was 3.6 months (range, 1 week to 10.5 months). Otoscopists participated as often as their schedules permitted, but commonly on a weekly basis.

Total and Mean Numbers of Examined Ears Required for Validation, According to Specialty

Specialist/Effusion Status of Ears Examined	No. of Ears Examined	
	Total	Mean
Otolaryngologist (N = 15)		
Effusion present	962	64
Effusion absent	717	48
Total	**1679**	**112**
Pediatrician (N = 12)		
Effusion present	953	79
Effusion absent	808	67
Total	**1761**	**146**
Pediatric Nurse Practitioner (N = 3)		
Effusion present	366	122
Effusion absent	341	114
Total	**707**	**236**
All Specialists (N = 30)		
Effusion present	2281	76
Effusion absent	1866	62
Total	**4147**	**138**

Sensitivity and Specificity

The mean sensitivity scores for the otolaryngologists, pediatricians, pediatric nurse practitioners, and the group of trainees as a whole were 88%, 87%, 87%, and 87%, respectively. Mean specificity scores for each of these groups were 75%, 73%, 74%, and 74%, respectively. For the group as a whole, 95% confidence intervals for mean sensitivity and mean specificity scores were 85% to 90% and 70% to 79%, respectively. When determining whether a trainee should be considered validated, we assessed prior level of experience, overall (mean) sensitivity and specificity, and the trend of improvement for each consecutive group of 50 ears that were examined. We noted, particularly, the sensitivity and specificity for the last group of 50 ears. Twenty-four otoscopists examined at least two groups of 50 ears. Comparison of their scores for the first group of 50 ears and for the final group of 50 ears revealed that mean sensitivity was 87% and 89%, respectively, and mean specificity increased from 64% to 77%. The mean change in specificity was statistically significant (*P*<.01).

COMMENT

We believe that pneumatic otoscopy is the preferred method of examining children for the presence or absence of middle-ear effusion. In a survey conducted in the Dallas (Tex) area, Nelson[1] found that 21% (14) of 67 pediatricians always performed pneumatic otoscopy on all patients and only 42% (28) of pediatricians always performed pneumatic otoscopy on patients with a history of otitis media. Moreover, it has been our experience that the level of otoscopic diagnostic accuracy varies substantially among clinicians. Cavanaugh[2] reported wide variation in the amount of positive pressure produced by an experienced pneumatic otoscopist. In addition, Clarke and colleagues[3] had shown earlier that even skilled pneumatic otoscopists used widely varying pressure pulses and pulse frequencies, and that the pressure pulses were much higher than needed to produce visible movement of normal tympanic membranes. It is not clear to what degree such discrepancies affect diagnostic accuracy. In our experience, however, errors related to inadequate pneumatic otoscopic technique, particularly among novices, contribute frequently to diagnostic inaccuracy.

Several authors[4-6] from this institution have briefly described and previously recommended otoscopic validation, particularly for clinical investigators studying otitis media. In a study assessing interobserver variability, Mains and Toner[7] found, as in our population, that 55% of the children (aged 20 months to 12 years) who were examined had "significant" middle-ear effusion at myringotomy. They reported sensitivities of 88% and 84%, and specificities of 90% and 84% for each of two pneumatic otoscopists.

In our population of children, clinicians appeared to be more accurate in diagnosing the presence than the absence of effusion. Several factors might have affected the sensitivity and specificity scores of our participants. Our population was selected and, in a normative population, mean sensitivity and specificity scores might differ. In addition, because otoscopists were aware that the children who were examined were about to undergo myringotomy with or without tympanotomy tube placement, expectation bias could have existed in some cases. Such a bias would tend to increase sensitivity and decrease specificity. During the orientation meetings, however, trainees were told that many children would be without effusion at the time of surgery.

We believe that there are several benefits to an otoscopic validation program. Most importantly, it can provide a reasonable estimate of otoscopic diagnostic accuracy—a requirement for clinical investigators studying otitis media. In addition, participation in such a program may improve otoscopic skill, particularly if immediate and specific feedback can be provided. An on-site validated otoscopist or tympanometer could be used for this purpose. In this program, during the follow-up meetings with the program director, an attempt was made to ascertain and resolve particular difficulties that the trainee may have been experiencing, for example, expectation bias. During these meetings, individual sensitivity and specificity scores were shared with the participant. In addition, participants could follow up, on their own, with the study nurse regarding the myringotomy findings for ears that were particularly difficult to diagnose. As noted also by Bluestone and Cantekin,[4] we found, for many participants, that sensitivity or specificity, or both, increased over time. Mean specificity scores for the group as a whole improved during participation in the program. Thus, the experience is, at least in part, educational.

There are some limitations of the program. The group of children studied does not represent a usual pediatric practice. Most of the children with fluid in the middle ear have otitis media with effusion, and relatively few have acute otitis media. The current program focuses on the participant's ability to detect the presence or absence of effusion but not necessarily other conditions such as retraction pockets or cholesteatomas. In addition, for some participants, especially those who have been in private practice, it is necessary to become familiar with the process. For instance, clinicians are not able to obtain a history and then combine these data with the physical examination, as they might do in practice. Finally, the administration of nitrous oxide (N_2O) can result in gas transport to the middle ear, which may affect the specificity.[8]

Given the otoscopist's other professional demands, participation in the program can be time-consuming. For example, during the study period, at least 19 other clinicians failed to complete the program. The mean time required to achieve validation reflected the availability of ears for examination, the amount of time the participant could spend, and the trainee's prior skill level. Occasionally, because of poor performance in the program, a trainee was advised to discontinue participation temporarily and to examine ears outside of this setting with a validated observer. Time to validation included, however, the period from initial participation to completion.

We have shown that a program that validates otoscopic diagnostic accuracy can be organized. It is our experience that the benefits of such a program are considerable.

CONCLUSION

Assessment of pneumatic otoscopic accuracy is important and feasible. A formal validation program in which otoscopic diagnoses are compared with myringotomy findings can document the achievement of a reasonable standard of otoscopic diagnostic accuracy. Because otitis media is prevalent in children, we encourage clinicians, medical educators, and, particularly, clinical investigators concerned with this problem to participate in an otoscopic validation program.

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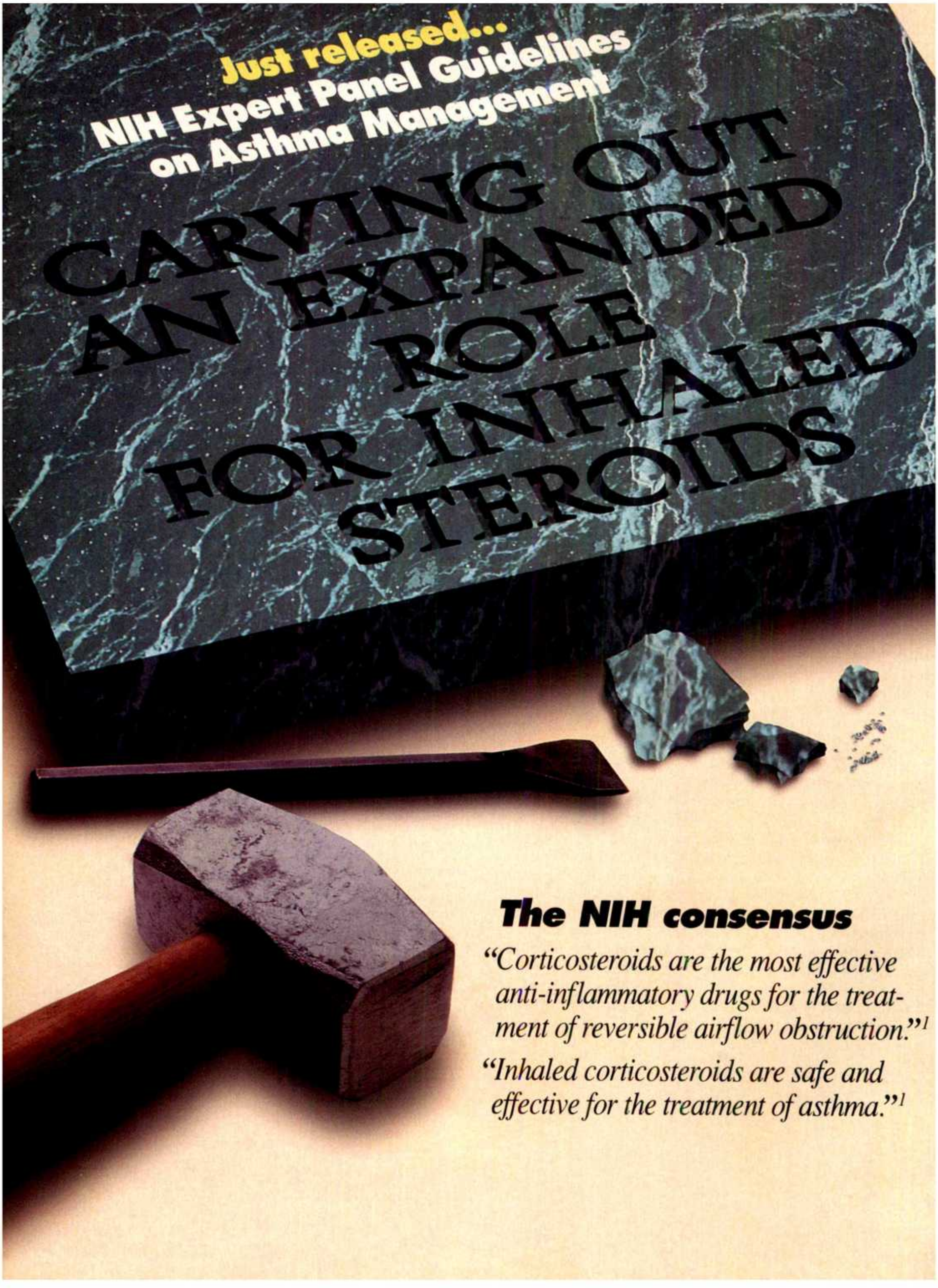

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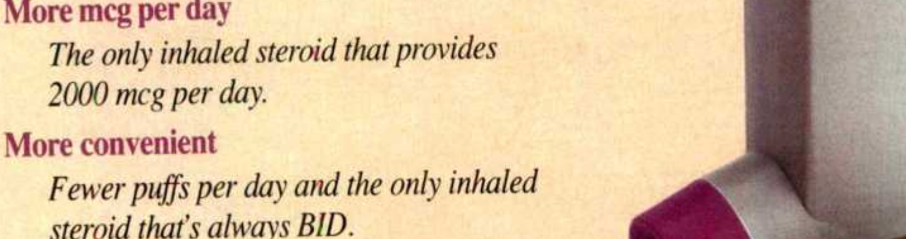

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CONTRAINDICATIONS

AeroBid Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with Candida albicans or Aspergillus niger have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral Candida may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler.

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function.

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice. An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors.

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General:* flu (10%); *Mouth and Throat:* sore throat (20%); *Nervous System:* headache (25%); *Respiratory:* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); *Special Senses:* unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations; *Gastrointestinal:* abdominal pain, heartburn; *General:* chest pain, decreased appetite, edema, fever; *Mouth and Throat:* Candida infection; *Nervous System:* dizziness, irritability, nervousness, shakiness; *Reproductive:* menstrual disturbances; *Respiratory:* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*; *Skin:* eczema, itching (pruritus), rash; *Special Senses:* ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; *Cardiovascular:* hypertension, tachycardia; *Gastrointestinal:* constipation, dyspepsia, gas; *Hemic/Lymph:* capillary fragility, enlarged lymph nodes; *Mouth and Throat:* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; *Nervous System:* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo; *Respiratory:* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort; *Skin:* acne, hives, or urticaria; *Special Senses:* blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath.

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*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

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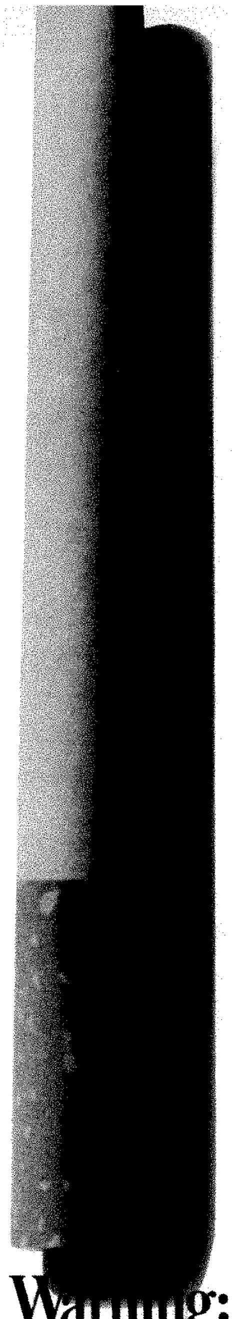

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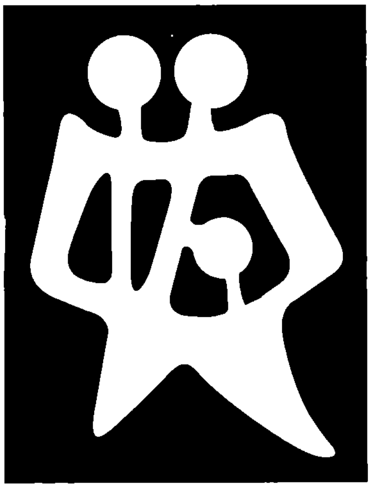

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APA Application for Membership

Information for Prospective Members

The objectives of the Ambulatory Pediatric Association are to improve the teaching of general pediatrics, to improve research in general pediatrics, to improve patient services in general pediatrics, and to affect public and governmental opinion regarding issues vital to teaching and research in general pediatrics. Applications for membership will be considered from members of the health care professions involved in teaching and patient care or research in general pediatrics.

Application forms are obtained from the Executive Secretary's Office:

Executive Secretary
Ambulatory Pediatric Association
6728 Old McLean Village Dr
McLean, VA 22101
(703) 556-9222

Future Annual Meetings

1993—*May 3-7, Sheraton Hotel, Washington, DC*
1994—*May 2-5, Seattle Convention Center, Seattle, Wash*
1995—*May 8-12, San Diego, Calif*
1996—*May 6-10, Washington, DC*
1997—*May 2-5, Washington, DC*

APA PROGRAM SCHEDULE

NOTE: Unless otherwise noted, all room numbers are located in the Baltimore Convention Center

Monday, May 4

Time	Event	Room
8:00 AM-5:00 PM	*APA Board of Directors*	Columbia (Hyatt Hotel)
7:30 PM-9:30 PM	*APA Committee Meetings*	
	Child Health Care Delivery	Room 312
	Research	Room 314
	Education	Room 316
	Public Policy	Room 311
	Communications	Room 313

Tuesday, May 5

Time	Event	Room
7:00 AM-8:30 AM	*APA Past Officers Breakfast*	Severn I (Sheraton Hotel)
8:00 AM-NOON	*APA Special Interest Groups*	
	Clerkship Directors	Room 307
	Emergency Medicine	Room 308
9:00 AM-NOON	*APA Special Interest Groups*	
	Adolescent Medicine	Room 318
	Women in Medicine	Room 320
	International Health	Room 301
	Residency Program Directors	Room 322
	Serving the Underserved	Room 312
	Pediatrics for Family Practice	Room 303
	APA Workshops 1-11	
	Workshop 1	Room 316
	Workshop 2	Room 311
	Workshop 3	Room 313
	Workshop 4	Room 315
	Workshop 5	Room 302
	Workshop 6	Room 304
	Workshop 7	Room 306
	Workshop 8	Room 319
	Workshop 9	Room 314
	Workshop 10	Room 323
	Workshop 11	Room 305
	APA Regional Chairs Luncheon	Severn II (Sheraton Hotel)
NOON-1:30 PM	*APA SIG Chairs Luncheon*	Sassafras (Sheraton Hotel)
	St. Geme Award Presentation	Hall A
1:00 PM-1:30 PM	*Joint Topic Sessions APA/APS/SPR (page 459)*	
1:30 PM-5:00 PM	Adolescent Medicine	Room 308
	Behavioral Pediatrics	Room 309
	Epidemiology and Preventive Pediatrics	Room 317
	General Pediatrics and Pediatric Education	Room 310
	Poster Session APA/APS/SPR Exhibits (page 462)	Hall B, C, D
5:00 PM-9:00 PM	*Opening Reception*	Hall B, C, D
8:00 PM-9:00 PM		

Wednesday, May 6

Time	Event	Room
7:15 AM-8:45 AM	*APA Regional Breakfast Meetings—Hyatt Hotel*	
	Region I	Camden/Lombard
	Region II	Columbia
	Region III	Chesapeake B
	Region IV	Baltimore
	Region V	Constellation F
	Region VI	Frederick
	Region VII	Annapolis
	Region VIII	Douglass
	Region IX	Chesapeake A
	Region X	Charles
9:00 AM-NOON	*APA Topic Plenary Sessions (page 481)*	
	Clinical Issues	Room 308
	Developmental & Behavioral Pediatrics	Room 301/303
	Emergency Medicine & Child Abuse	Room 309
	General Pediatrics	Room 310
	Prevention & Epidemiology	Room 307
1:30 PM-4:30 PM	*APA Special Interest Groups*	
	AIDS	Room 315
	Child Abuse	Room 302
	Injury Control	Room 304
	Primary Care	Room 306

APA Program Schedule

Time	Event	Room
	APA Workshops 12-20	
	Workshop 12	Room 320
	Workshop 13	Room 322
	Workshop 14	Room 312
	Workshop 15	Room 314
	Workshop 16	Room 313
	Workshop 17	Room 316
	Workshop 18	Room 311
	Workshop 19	Room 305
	Workshop 20	Room 318
4:45 PM-6:30 PM	*APA Business Meeting*	Constellation
	Research Award	Ballroom A
	Teaching Award	(Hyatt Hotel)
6:30 PM-7:30 PM	*APA Reception*	Columbia/Frederick/Annapolis (Hyatt Hotel)
8:30 PM-10:00 PM	*APA Debate*	Constellation Ballroom A (Hyatt Hotel)

Thursday, May 7

Time	Event	Room
8:00 AM-12:30 PM	*APA General Plenary Session (page 493)*	Room 309
	APA Presidential Address	
	APA George Armstrong Lecture	
2:00 PM-5:00 PM	*APA Special Interest Groups*	
	Behavior/Chronic Illness	Room 321
	Continuity Clinic	Room 301
	Day Care	Room 320
	Homeless Children	Room 322
	Nutrition	Room 312
	Division Directors in General Pediatrics	Room 318
	Inpatient General Pediatrics	Room 302
	APA Workshops 21-30	
	Workshop 21	Room 314
	Workshop 22	Room 316
	Workshop 23	Room 311
	Workshop 24	Room 313
	Workshop 25	Room 319
	Workshop 26	Room 323
	Workshop 27	Room 304
	Workshop 28	Room 306
	Workshop 29	Room 315
	Workshop 30	Room 303

Friday, May 8

Time	Event	Room
8:00 AM-1:00 PM	APA Board of Directors Meeting	Constellation C (Hyatt Hotel)

Registration Hours

Sunday, May 3	NOON-5:00 PM
Monday, May 4	8:00 AM-10:00 PM
Tuesday, May 5	7:00 AM-9:00 PM
Wednesday, May 6	7:00 AM-5:30 PM
Thursday, May 7	7:00 AM-5:00 PM

Workshop Registration

Tuesday, May 5	7:00 AM-5:00 PM
Wednesday, May 6	7:00 AM-5:30 PM
Thursday, May 7	7:00 AM-5:00 PM

The California State Board of Registered Nursing has approved this program for 23 Continuing Education Credits for Registered Nurses. Certificates will be available at the APA registration desk.

The 1992 combined meetings of the American Pediatric Society, The Society for Pediatric Research, and the Ambulatory Pediatric Association will be jointly sponsored by the Johns Hopkins University School of Medicine. The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The Johns Hopkins University School of Medicine designates this continuing medical education activity for up to 37.5 credit hours in Category I of the Physician's Recognition Award of the American Medical Association.

Sign in sheets and request forms for individuals desiring confirmation of continuing education credit hours will be available at the APS/SPR/APA Meeting Registration Desk at the Baltimore Convention Center in Baltimore, Md. There is a $15 charge for the CME certificate. Forms may also be obtained by contacting:

The APS/SPR Program Office
141 Northwest Point Blvd
PO Box 675
Elk Grove Village, IL 60009-0675
(708) 427-0205

Ambulatory Pediatric Association 1991-1992

Officers

President	*Kathleen G. Nelson, MD,* Birmingham, Ala
President-Elect	*Modena E. H. Wilson, MD, MPH,* Baltimore, Md
Secretary-Treasurer	*Thomas G. DeWitt, MD,* Worcester, Mass
Immediate Past President	*Carol Berkowitz, MD,* Torrance, Calif
Communications Director	*John M. Pascoe, MD, MPH,* Madison, Wis

Board of Directors

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John M. Leventhal, MD, New Haven, Conn
Stephen Ludwig, MD, Philadelphia, Pa
Lucy Osborn, MD, Salt Lake City, Utah
Judith S. Palfrey, MD, Boston, Mass
James Seidel, MD, Phd, Torrance, Calif

Past Presidents

1961-1962	*Richard W. Olmsted*
1962-1963	*Morris Green*
1963-1964	*Robert J. Haggerty*
1964-1965	*Frederic M. Blodgett*
1965-1966	*Donal Dunphy*
1966-1967	*Loren G. MacKinney*
1967-1968	*Lewis M. Fraad*
1968-1969	*Hugo Dunlap Smith*
1969-1970	*Joel J. Alpert*
1970-1971	*John H. Kennell*
1971-1972	*Donald Fink*
1972-1973	*Ray E. Helfer*
1973-1974	*Katherine S. Lobach*
1974-1975	*Evan Charney*
1975-1976	*Frederick North, Jr.*
1976-1977	*Margaret C. Heagarty*
1977-1978	*Robert Hoekelman*
1978-1979	*George Comerci*
1979-1980	*Ivan Barry Pless*
1980-1981	*Barbara Starfield*
1981-1982	*Alvin Novack*
1982-1983	*Philip Nader*
1983-1984	*Fredric D. Burg*
1984-1985	*Abraham B. Bergman*
1985-1986	*Catherine DeAngelis*
1986-1987	*Jay E. Berkelhamer*
1987-1988	*Ruth E. K. Stein*
1988-1989	*Steven P. Shelov*
1989-1990	*Paul McCarthy*
1990-1991	*Carol Berkowitz*

Regional Chairs

I.	*Anthony Alario, Jr., MD,* Providence, RI
II.	*Mary Ann LoFrumento, MD,* Morristown, NJ
	Alan B. Bernstein, MD, Brooklyn, NY
III.	*Kenneth M. McConnochie, MD,* Rochester, NY
IV.	*Gregory Hayden, MD,* Charlottesville, Va
V.	*Daniel Coury, MD,* Columbus, Ohio
	John Chessare, MD, MPH Toledo, Ohio
VI.	*Patricia S. Simmons, MD,* Rochester, Minn
	Timothy Russell Schum, MD, Milwaukee, Wis
VII.	*Pamela Wood, MD,* San Antonio, Tex
VIII.	*Gerald Hickson, MD,* Nashville, Tenn
	Joseph Pesek, MD, Jacksonville, Fla
IX.	*Lawrence C. Kleinman, MD,* Los Angeles, Calif
	Stanley Howard Inkelis, MD, Los Angeles, Calif
X.	*Kathi Kemper, MD,* Seattle, Wash

Past Secretary-Treasurers

1961-1963	*Frederic M. Blodgett*
1963-1966	*Hugo Dunlap Smith*
1966-1969	*Abraham B. Bergman*
1969-1972	*Katherine S. Lobach*
1972-1974	*Elizabeth S. Hillman*
1974-1977	*George Comerci*
1977-1980	*Fredric D. Burg*
1980-1983	*Barbara Durand*
1983-1986	*Marie McCormick*
1986-1989	*Kathleen Nelson*

APA Teaching Award

The purpose of this award is to foster interest in the teaching of ambulatory pediatrics by giving national recognition to an outstanding ambulatory pediatric program. Programs must demonstrate excellence in educational teaching methods, acceptance by students and/or residents, acceptance by the community and the institution, innovations and adaptability, or outstanding quality of the individuals trained in the program. Emphasis is placed on the award being given to *an* outstanding *program.*

1972 University of Arizona
College of Medicine
Department of Pediatrics
Division of Ambulatory Pediatrics
Tucson

1976 University of Chicago
Pritzker School of Medicine
Wyler Children's Hospital
Division of Ambulatory Pediatrics

1977 University of Vermont College of Medicine
Department of Pediatrics
Division of Ambulatory Pediatrics
Burlington, Vt

1978 Children's Hospital of Philadelphia
Division of Ambulatory Services
Resident Group Practice

1980 Primary Care Training Program
Department of Pediatrics
University of Arizona
College of Medicine
Tucson

1981 Sinai Hospital of Baltimore
Pediatric Residency Training Program

1982 Child Health Associate Program
University of Colorado
Health Sciences Center
Denver

1984 University of North Carolina at Chapel Hill
Department of Pediatrics
Community Outreach Training Program

1986 Pediatric Practice Model
University of Oklahoma College of Medicine
Oklahoma City

1987 Chronic Illness Teaching Program
Department of Pediatrics and
Human Development
Michigan State University
East Lansing

1988 Emergency Room Teaching Program
Children's Hospital of Philadelphia
and
Behavioral and Developmental
Pediatric Fellowship Program
Department of Pediatrics
Ohio State University
Columbus

1989 Primary Care Training Program
University of California,
San Diego
Department of Pediatrics
Division of General Pediatrics

1990 Behavioral Science Training Program
University of California,
San Francisco

1991 University of Utah Pediatric Residency Program
University of Utah Center for Health Sciences
and the Primary Children's Medical Center
Salt Lake City
and
Third Year Pediatric Clerkship (MS III)
Department of Pediatrics
F. Edward Hebert School of Medicine
Uniformed Services University of the
Health Sciences
Bethesda, Md

1992 Integrated Medical Education Programs
of the Department of Pediatrics
University of Massachusetts Medical Center
Worcester

APA Awards

APA RESEARCH AWARD

The APA Research Award acknowledges the contribution of an individual in advancing pediatric knowledge through excellence in research. Research excellence is characterized by originality, creativity, and methodological soundness. The findings should contribute significantly to the general health of children in such areas as understanding mechanisms of health and disease, methods of education, and innovative ways of providing children's services.

1990 ***Barbara Starfield***

1991 ***Ivan Barry Pless***

1992 ***Frederick P. Rivara***

APA DISTINGUISHED CAREER AWARD

The APA Distinguished Career Award recognizes members of the Association who have fostered the goals of the APA throughout their careers. They have distinguished themselves in the promotion of improved patient care, teaching, and research in ambulatory pediatrics.

1991 ***Barbara M. Korsch***

The George Armstrong Lecture

George Armstrong, an English physician of the 18th century, established the first dispensary for children in London, England, in 1769. There he served with great devotion and taught others the care of sick children. He is honored as one of the fathers of modern pediatrics, and those who deliver this lecture are also honored as outstanding teachers and contributors to our knowledge of the care of children.

The lecture is sponsored by Ross Laboratories, Columbus, Ohio.

1967	George A. Silver
1968	Allan M. Butler
1969	Robert H. Haggerty
1970	Julius B. Richmond
1971	Morris Green
1972	Henry K. Silver
1973	Barbara M. Korsch
1974	Lewis Fraad
1975	C. Henry Kempe
1976	Abraham B. Bergman
1977	Wilbur J. Cohen
1978	Richard W. Olmsted
1979	John H. Kennell
1980	OXFAM (Tim Lusty)
1981	Benjamin Spock
1982	Evan Charney
1983	Barbara Starfield
1984	Victor Vaughan Waldo Nelson
1985	Gerold L. Schiebler
1986	Marian Wright Edelman (Children's Defense Fund)
1987	Robert A. Hoekelman
1988	Ivan Barry Pless
1989	Joel J. Alpert
1990	Catherine DeAngelis
1991	Paul L. McCarthy
1992	Children's Television Workshop (David V. B. Britt)

APA Workshops

SESSION I

Tuesday, May 5, 9 AM-NOON

NOTE: All APA Workshops will be held in the Baltimore Convention Center in the rooms indicated.

1. **Avoiding Common Statistical Errors: A Dermatologic Approach** *Room 316*

   Leader: *T. B. Newman*
2. **Patient Reports About Quality of Care: What Does the Consumer Think?** *Room 311*

   Leaders: *C. Homer, D. Goldmann, and E. Rhinehart*
3. **Parents as Case Managers of Their Children With Special Health Care Needs** *Room 313*

   Leaders: *R. Goldman, A. Diano, R. Cruz, S. Ault, and R. E. K. Stein*
4. **Teaching Behavioral Pediatrics Through Resident Continuity Clinics** *Room 315*

   Leaders: *D. L. Coury, T. Stancin, S. Lesure, T. Linscheid, S. Walker, and G. French*
5. **The AIDS Epidemic: Strategies for Behavioral Change in Pre-Adolescents and Adolescents** *Room 302*

   Leaders: *S. Feigelman, B. Stanton, I. Ricardo, M. Black, V. Keane, L. Kaljee, and J. Galbraith*
6. **Teaching Skills for Community Preceptors: A Faculty Development Model** *Room 304*

   Leaders: *T. G. DeWitt, R. L. Goldberg, and K. Roberts (1992 APA Teaching Award Recipient)*
7. **Put Prevention Into Practice: Teaching Prevention to Residents and Students** *Room 306*

   Leaders: *D. Kamerow, C. DiGuiseppi, L. Dickey, and P. Nutting*
8. **Ethics in Acute Care Medicine: An Approach Under Stressful Circumstances** *Room 319*

   Leaders: *B. King, L. Bell, S. Ludwig, J. Wiley, S. Selbst, and J. Loiselle*
9. **Decision Analysis: Principles and Practice** *Room 314*

   Leaders: *S. M. Downs and T. A. Lieu*
10. **Issues in the Detection of Family Violence in Primary Care** *Room 323*

    Leaders: *R. Chernoff, L. McKibben, and L. Wissow*
11. **Project School Care: Establishing Pediatric Consultation Programs in the Community** *Room 305*

    Leaders: *J. S. Palfrey, L. Haynie, S. Porter, and T. Bierle*

SESSION II

Wednesday, May 6, 1:30 PM-4:30 PM

12. **On the Street Where You Live: Coping with Gangs in the 90's** *Room 320*

    Leaders: *L. S. Fitzmaurice and J. F. Knapp*
13. **Pediatricians' Facilitation of Healthy Sexual Development With Families** *Room 322*

    Leader: *C. A. Croft*
14. **Making Things Better: How to Develop Programs in Pediatrics** *Room 312*

    Leaders: *C. L. J. Bauman and R. E. K. Stein*
15. **A Model Program in Faculty Research Development and Facilitation** *Room 314*

    Leaders: *C. D. Baldwin, D. K. Rassin, and H. G. Levine*
16. **School-Based Adolescent Health Care** *Room 313*

    Leaders: *M. Fisher, J. G. Lear, L. Juszczak, and S. B. Friedman*
17. **Stayin' Alive in Pediatric Emergency Medicine, Part II: The Solutions** *Room 316*

    Leaders: *S. Selbst, F. Henretig, S. Ludwig, K. Shaw, J. Lavelle, D. Baker, L. Bell, J. Maller, and C. McAneney*
18. **All About Getting a Research Grant: Perspectives from Federal Funding Agencies, Private Funding Agencies and Study Section Reviewers** *Room 311*

    Leaders: *R. T. Gross, R. Haggerty, W. Kessel, P. McCarthy, J. Palfrey, R. Pantell, and S. Yaffe for the APA Research Committee*
19. **Using a Collaborative Project for Fellowship Training in Research** *Room 305*

    Leaders: *A. K. Duggan, J. Serwint, M. Wilson, and Fellows*
20. **Anatomy and Physiology of Successful Pediatric Training Programs: What We Can Learn and Apply Back Home** *Room 318*

    Leaders: *J. M. Devries, L. Osborn, G. Cantor, and M. Bar-on*

SESSION III

Thursday, May 7, 2 PM-5 PM

21. **Culture & Clinical Care: Providing Services in the Multicultural Setting** *Room 314*

    Leaders: *L. M. Pachter, H. Egan, G. Burke, W. G. Bithoney, and APA SIG Serving the Underserved*
22. **Developing High Quality Practice Guidelines** *Room 316*

    Leaders: *C. Z. Margolis, J. Cooley, and J. Urkin*
23. **The Pediatric Emergency Department and the Community Pediatrician: A Working Relationship Revisited** *Room 311*

    Leaders: *R. Kulick, E. Doyne, G. DiGiulio, M. Stephan, M. Murray, and R. Ruddy*
24. **Measuring Child Health Status for Research and Patient Care** *Room 313*

    Leaders: *E. Schor and J. Landgraf*
25. **A Pediatric Clerkship for the 21st Century** *Room 319*

    Leaders: *F. A. McCurdy, C. B. White, J. O. Lopreiato, B. A. DeFrancesco, and M. C. Ottolini*
26. **Colposcopy for the Beginner** *Room 323*

    Leaders: *J. Kelly, J. Knapp, and B. Arnold-Biagioli*
27. **Group Will Child Care in At Risk Populations** *Room 304*

    Leaders: *E. A. Nicholas, K. Kemper, L. M. Osborn, L. Messenger, and M. Sifuentes*
28. **Preparing Interns for Residency: A "Teaching and Leadership" Seminar** *Room 306*

    Leaders: *J. Anderson, C. Chantry, R. Kamei, and K. Overby*
29. **The Bottom Line: Making the Pediatric Emergency Department Financially Sound** *Room 315*

    Leaders: *S. Selbst, S. Ludwig, J. Lavelle, M. A. Murray, J. Loiselle, and N. Kunkel*
30. **Technology in Teaching: Medical Photography** *Room 303*

    Leaders: *M. E. Bar-on and A. T. Jones*

With American Pediatric Society and Society for Pediatric Research

Tuesday, May 5, 1:30 PM-5:00 PM

ADOLESCENT MEDICINE

Room 308 Convention Center

Moderators: *Hoover Adger, Jr., MD, Paul Dyment, MD, and Mary Ann B. Shafer, MD*

1:30 ***Resting Heart Rate and Obesity Are Related to Elevated Cardiovascular Risk Factor Levels in Adolescent Females.** *M. R. Arden, D. Hardoff, J. Feldman, L. Altshuler, H. Shaw, N. Cooperman, I. R. Shenker, and M. S. Jacobson. Department of Pediatrics, Albert Einstein College of Medicine, Long Island Jewish Medical Center, Schneider Children's Hospital.*

1:45 ***Cardiovascular Risk Factors in an Urban Multiethnic High School Population.** *D. Hardoff, M. R. Arden, N. M. Cooperman, H. Shaw, L. Altshuler, J. Feldman, I. R. Shenker, and M. S. Jacobson. Department of Pediatrics, Albert Einstein College of Medicine, Long Island Jewish Medical Center, Schneider Children's Hospital.*

2:00 ***Can Dietary Calcium Supplementation Improve Pubertal Girls' Growth and Bone Mineral Status?** *G. M. Chan, K. Hoffman, and M. McMurry. Department of Pediatrics, University of Utah.*

2:15 ***Sex Steroid Hormone Distribution and Body Composition in Young Women.** *A. C. Hergenroeder, C. M. White, W. J. Klish, C. Bender, R. A. Hajek, and L. A. Jones. Department of Pediatrics, Baylor College of Medicine, and Department of Gynecology, M. D. Anderson Cancer Center, Houston.*

2:30 ***Adolescents with Anorexia Nervosa (AN) Demonstrate Abnormal Calcium Balance and Decreased Bone Ca Flow.** *S. Abrams, T. Silber, N. Esteban, N. Vieira, R. Meyers, N. Bell, J. Shary, and A. Yergey. USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, Tex; LTPB/NICHD, Bethesda, Md; Department of Adolescent Medicine, Children's National Medical Center, Washington, DC; and University of South Carolina, Charleston.*

2:45 **Breast Feeding Attitudes and Practices Among Adolescents.** *M. Neifert, S. DeMarzo, J. Seacat, and C. Darden. Lactation Program, Presbyterian-St. Luke's Medical Center, Denver, Colo.*

3:00 ***Predicting Child Maltreatment Among Children of Teenage Mothers.** *P. Flanagan, S. Riggs, L. Andreozzi, and C. G. Coll. Department of Pediatrics, Women and Infants, Brown University and Rhode Island Hospitals.*

3:15 ***Impact of Alcohol Availability on Adolescent Automobile Fatalities.** *K. J. Kelleher, V. I. Rickert, R. S. Kirby, and M. Kashner. Department of Pediatrics, University of Arkansas for Medical Sciences, and Arkansas Children's Hospital.*

3:30 **Predictors of Depression and Parenting Stress in Pregnant Teens.** *T. M. Kohlenberg and J. P. Shonkoff. Departments of Pediatrics, Boston (Mass) University School of Medicine, and University of Massachusetts Medical School, Worcester.*

3:45 **The Meaning of Traumatic Injury and Death Among Adolescents in an American Indian Community.** *D. C. Grossman, R. W. Putsch, and T. S. Inui. Departments of Medicine and Pediatrics, University of Washington, Seattle.*

4:00 ***Determinants of Condom Use in Adolescent Males at Risk for STD.** *D. P. Orr and C. D. Langefeld. Department of Pediatrics, Indiana University School of Medicine, Indianapolis.*

4:15 ***Impaired Growth in HIV Positive Transfused Hemophiliacs Is Related to Maturational Delay.** *J. M. Gertner, F. R. Kaufman, S. M. Donfield, L. A. Sleeper, M. W. Hilgartner, and the Hemophilia Growth and Development Study (HGDS). New York Hospital; Cornell Medical Center; Children's Hospital of Los Angeles; and New England Research Institute, Watertown, Mass.*

4:30 ***Single Dose Azithromycin for the Treatment of Genital Chlamydial Infection in Adolescent Women.** *M. R. Hammerschlag, N. Golden, M. Gelling, Z. Aras, W. Dumornay, and P. Roblin. SUNY Health Science Center at Brooklyn, and Department of Pediatrics, Brookdale Hospital Medical Center.*

4:45 **Adolescents' Knowledge, Attitudes and Behavior About Skin Cancer Prevention.** *L. Mitan and R. M. Cavanaugh. Department of Pediatrics, SUNY Health Science Center, Syracuse.*

BEHAVIORAL PEDIATRICS

Room 309 Convention Center

Moderators: *Thomas Boyce, MD, William B. Carey, MD, and Cynthia T. Garcia Coll, MD, PhD*

1:30 ***CSF Monoamine Precursors and Metabolites in Human Neonates Following In Utero Cocaine Exposure.** *R. Needlman, B. Zuckerman, G. Anderson, M. Mirochnick, and D. Cohen. Boston University School of Medicine; Department of Pediatrics, Boston City Hospital; and Yale Child Study Center, Yale University School of Medicine.*

1:45 ***Alcohol and Cigarette Use During Pregnancy and Newborn Outcome.** *B. M. Lester, J. K. Nugent, S. Greene, and Dorit-Wieczorek-Deering. Brown University and University of Massachusetts, Amherst.*

2:00 ***Maternal Pre-Eclampsia and Infant Temperament.** *R. Hagan, S. Evans, H. Benninger, N. French, J. Newnham, and W. McDonald. Departments of Newborn Services and Obstetrics, King Edward Memorial Hospital, Perth, Australia.*

2:15 **Calming Effect of Intraoral Sucrose in Crying Six Week Olds.** *R. G. Barr, D. Cousineau, T. F. Oberlander, J. A. Brian, and S. N. Young. Departments of Pediatrics and Psychiatry, McGill University, Montreal, Quebec, and Montreal Children's Hospital.*

2:30 **Screening Mothers for Depression.** *K. Kemper and T. Babonis. Department of Pediatrics, Harborview Medical Center, Seattle, Wash.*

2:45 **Maternal Social Support and Child Care Problem-Solving Skills: Is There an Association?** *J. M. Pascoe and K. Pridham. Department of Pediatrics and School of Nursing, University of Wisconsin, Madison.*

3:00 ***Specificity of Preventive Pediatric Intervention Effects in the Newborn Period.** *M. J. Beeghly, K. A. Flannery, J. K. Nugent, T. B. Brazelton, and E. Z. Tronick. Harvard Medical School and Children's Hospital, Boston.*

3:15 ***Comparison of Fathers and Doulas as Supportive Labor Companions.** *B. C. Lohn, J. H. Kennell, and S. K. McGrath. Case Western Reserve University, Cleveland, Ohio.*

3:30 **Do Foster Parents Do It for the Money?** *D. M. Brazdziunas, C. A. Gosselink, A. Kresheck, and E. Ekwo. Department of Pediatrics, University of Chicago, Ill, and La Rabida Children's Hospital, Chicago.*

3:45 ***3 Year Outcomes of Children Who Develop Failure to Thrive During Infancy in a Low Birth Weight Preterm Cohort.** *P. H. Casey, K. J. Kelleher, R. Bradley, S. K. Pope, L. Whiteside, K. Barrett, and M. E. Swanson. Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock.*

4:00 ***Childcare Stressors, Cardiovascular Reactivity and Injury Incidence in Preschool Children.** *W. T. Boyce, M. Chesney, P. Kaiser, A. Alkon-Leonard, and J. Tschann. Departments of Pediatrics and Epidemiology/Biostatistics, University of California, San Francisco.*

4:15 ***"Goodness of Fit" And Developmental Outcome in Term and Preterm Infants.** *B. M. Lester, C. F. Z. Boukydis, C. Garcia-Coll, M. McGrath, B. Vohr, and F. Brem. Brown University; E. P. Bradley Hospital; and Women & Infants Hospital, Providence, RI.*

4:30 ***Adaptation to Childhood Cancer: Sibling Psychologic Distress.** *O. J. Z Sahler, K. J. Roghmann, P. J. Carpenter, R. K. Mulhern, M. J. Dolgin, J. R. Sargent, O. A. Barbarin, D. R. Copeland, and L. K. Zeltzer. University of Rochester School of Medicine, St. Jude Children's Research Center, Memphis, Tenn; Los Angeles Children's Hospital; University of Utah School of Medicine; University of Michigan, Ann Arbor; M. D. Anderson Cancer Center, Houston; and UCLA.*

4:45 **Training in Behavioral Pediatrics Does Make A Difference!**

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*Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, *Pediatric Research, April 1992.*

J. M. Leventhal, S. M. Horwitz, P. Leaf, K. Speechley, and B. Forsyth. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

Room 317 Convention Center

Moderators: *Ruth Etzel, MD, Leon Gordis, MD, and Katherine K. Christofell, MD, MPH*

1:30 **The Epidemiology of Medically Attended Non-Fetal Injuries in Children and Youth from a Nationally Representative Sample.** *P. Scheidt, Y. Harel, D. Jones, M. Overpeck, and P. Bijur. National Institute of Child Health and Human Development, Bethesda, Md; Division of Adolescent and School Health, Centers for Disease Control, Atlanta, Ga; and Albert Einstein College of Medicine, Bronx, NY.*

1:45 **Age-Specific Prevalence Trends for Selected Hymenal Findings in Suspected Child Sexual Abuse Victims.** *D. L. Kerns, M. L. Ritter, and T. Leong. Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, Calif.*

2:00 ***Comprehensive Evaluation of Pediatric Vaccine Safety: The Use of Computer Databases to Assess Emergency, Outpatient and Hospital Utilization in Three Health Maintenance Organizations.** *S. Black, H. Shinefield, J. Mullooly, W. Barlow, T. Payne, R. Thompson, R. Chen, J. Glasser, and S. Wassilak. The Northern California and Northwest Region Kaiser Permanente Group Health Cooperative of Puget Sound and the Center for Disease Control.*

2:15 ***Decrease in Admissions for Invasive Haemophilus Influenzae Type B (HIB) Disease Among Children of U.S. Army Active Duty Personnel, 1984-1991.** *L. E. Broadhurst and R. L. Erickson. Walter Reed Army Institute of Research, Division of Preventive Medicine, Washington, DC.*

2:30 ***Comparison of Thirteen Acellular Pertussis Vaccines: Adverse Reactions (RXN).** *M. D. Decker, K. M. Edwards, M. C. Steinhoff, M. B. Rennels, M. E. Pichichero, J. A. Englund, E. L. Anderson, M. A. Deloria, G. F. Reed, and the NIAID Acellular Pertussis Vaccine Study Group. Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.*

2:45 ***Urinary Tract Infections (UTIS) and the Uncircumcised State: A Meta-Analysis.** *T. E. Wiswell and W. E. Hachey. Department of Pediatrics, Walter Reed Army Medical Center, Washington, DC.*

3:00 ***Urinary Tract Infections (UTIS) and the Uncircumcised State: An Update.** *T. E. Wiswell and W. E. Hachey. Department of Pediatrics, Walter Reed Army Medical Center, Washington, DC.*

3:15 ***Decrease in the Average Blood Lead (BPb) in a Population of Lower Middle Class Urban Children Between 1985 and 1991.** *S. Piomelli, E. Flaster, C. Seaman, and D. Carriero. Division of Pediatric Hematology, Columbia University College of Physicians and Surgeons.*

3:30 ***Bone Lead (Pb) Content by L-X-Ray Fluorescence (LXRF) in Three Populations Exposed to Different Amounts of Pb.** *M. E. Markowitz and J. F. Rosen. Department of Pediatrics, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY.*

3:45 **Factors Associated with Tuberculosis Risk in Poor Urban Children.** *C. D. Courtlandt, B. P. Dreyer, A. H. Fierman, R. Lawrence, J. Rivera, P. Ryan, L. Au, L. Legano, and J. Guttenberg. Department of Pediatrics, New York (NY) University School of Medicine.*

4:00 ***The Risk of HIV-1 Infection in Children Born to HIV-Infected Women with Serial Pregnancies.** *B. J. Simpson, W. A. Andiman, and E. D. Shapiro. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.*

4:15 **Fetal Outcomes of Pregnancies in Women with Delayed Childbearing.** *M. B. Aldous and M. B. Edmonson. Department of Epidemiology, University of Washington, Seattle.*

4:30 ***Seasonal Changes in Weight for Age in a Pediatric Emergency Room: Potential Source of Bias in the NHANES.** *D. A. Frank, M. Napoleone, A. Meyers, N. Roos, K. Peterson, and L. A. Cupples. Departments of Pediatrics and Public Health, Boston (Mass) University; School of Public Health, Harvard University; and Department of Pediatrics, Boston City Hospital.*

4:45 ***Nutrient Quality of Fat and Cholesterol Modified Diets of Hyperlipidemidic Children and Adolescents.** *N. Copperman, J. Schebendach, M. R. Arden, C. Eisenberg, and M. S. Jacobson. Department of Pediatrics, Albert Einstein College of Medicine, Long Island Jewish Medical Center, Schneider Children's Hospital, Bronx, NY.*

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

Room 310 Convention Center

Moderators: *Evan Charney, MD, Gregory F. Hayden, MD, and Diane Kittredge, MD*

1:30 **Management of Childhood Lead-Poisoning: Clinical Impact and Cost-effectiveness.** *D. Glotzer, K. Freedberg, and H. Bauchner. Departments of Pediatrics and Medicine, Boston (Mass) University School of Medicine, and Boston City Hospital.*

1:45 ***Limited Prognostic Value of Post-Treatment Throat Culture for Group A Beta-Hemolytic Streptococcus (GABHS).** *D. M. Keller, J. L. Paradise, D. K. Colborn, and S. M. Caputo. University of Pittsburgh (Pa) School of Medicine, and Department of Pediatrics, Children's Hospital of Pittsburgh.*

2:00 ***Comparative Efficacy of Tonsillectomy for Recurrent Throat Infection in More vs Less Severely Affected Children.** *J. L. Paradise, C. D. Bluestone, K. D. Rogers, F. H. Taylor, D. K. Colborn, B. S. Bernard, and R. Z. Bachman. University of Pittsburgh (Pa) School of Medicine, and Department of Pediatrics, Children's Hospital of Pittsburgh.*

2:15 ***The Acute Treatment of Croup with Aerosolized Dexamethasone.** *D. Johnson, S. Schuh, G. Koren, and D. Jaffe. Divisions of Emergency Services and Clinical Pharmacology/Toxicology, The Hospital for Sick Children, University of Toronto.*

2:30 ***Efficacy of Oral Prednisone (OP) in the Emergency Room Treatment of Acute Asthma in Children.** *R. J. Scarfone, S. Fuchs, A. L. Nager, and S. A. Shane. University of Pittsburgh (Pa) School of Medicine, and Department of Pediatrics, Children's Hospital of Pittsburgh.*

2:45 ***A Prospective, Double-Blind, Randomized Comparison of Intramuscular Meperidine and Promethazine, With and Without Chlorpromazine.** *T. E. Terndrup, C. M. Madden, D. J. Dire, D. Gavula, and R. M. Cantor. Departments of Pediatrics and Emergency Medicine, SUNY Health Science Center at Syracuse and University Hospital.*

3:00 ***Is an Emergency Department Visit A Marker of Undervaccination (UV)?** *L. E. Rodewald, P. G. Szilagyi, S. G. Humiston, R. F. Raubertas, K. J. Roghmann, L. A. Cove, C. B. Doane, and C. B. Hall. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*

3:15 **Preventive Pediatric Health Care: A New Measurement Tool.** *J. Brown, P. Melinkovich, and S. A. Ricketts. Department of Community Health, Denver (Colo) Health and Hospitals, and Community Health Service Division, Colorado Department of Health, Denver.*

3:30 **Prenatal Pediatric Visits: Implementation in a Pediatric Ambulatory Department by Pediatric Residents.** *P. Heald, K. Benedum, and B. Bradford. Department of Pediatrics, The Mercy Hospital of Pittsburgh, Pa.*

3:45 **Gender Differences in Pediatrician Communication During Primary Care.** *M. E. H. Wilson, L. S. Wissow, and D. Roter. Department of Pediatrics and Health Policy and Management, The Johns Hopkins University, Baltimore, Md.*

4:00 ***Increasing Prevalence of Medical Technology Dependency Among Children: Results of 1987 and 1990 Census in Massachusetts.** *J. S. Palfrey, L. Haynie, S. Porter, T. Bierle, B. Johnson, T. Fenton, and P. Cooperman. Children's Hospital, Boston, Mass.*

4:15 ***Who Makes Medication Order Errors in a Residency Training Program?** *S. B. Manoff, J. A. McMillan, C. K. Lee, V. L. Bradley, and F. A. Oski. The Johns Hopkins University, Baltimore, Md.*

4:30 **An Environmental Intervention to Reduce the Fat Content of School Lunches.** *R. C. Whitaker, J. A. Wright, A. J. Finch, and B. M. Psaty. Departments of Pediatrics and Medicine, Epidemiology and Health Services, School of Medicine and Public Health and Community Medicine, University of Washington, Seattle.*

4:45 ***Intervention Trial in Children for Early prevention of Atherosclerosis: Preliminary Results.** *H. Kovanen, E. Jokinen, A. Myyrinmaa, J. Viikari, T. Ronnemaa, I. Valimaki, T. Routi, J. Venetoklis, O. Hollo, P. Salo, and O. Simell. Cardiorespiratory Research Unit, Departments of Pediatrics and Medicine, University of Turku, Finland, and Rehabilitation Research Center of the Social Insurance Institute, Turku.*

Tuesday, May 5
5:00 PM-9:00 PM
Exhibit Hall B, C, D
Convention Center

ADOLESCENT MEDICINE

1. **Gender Differences Among Incarcerated Adolescents on STD Related Attitudes and Behaviors.** *K. D. Reynolds, M. K. Oh, G. Cloud, J. Reynolds, and D. Ogden. Department of Pediatrics, University of Alabama at Birmingham.*
2. **Prevention of Chlamydial Infections in Infants Born to Teen Mothers.** *M. Melzer-Lange, L. Good, and H. Hennes. Department of Pediatrics and Teen Pregnancy Service, Medical College of Wisconsin, Milwaukee.*
3. **Effective Health Services for Adolescents: Developing a National Census of Comprehensive Services.** *J. D. Klein, G. H. DeFriese, M. Kotelchuck, F. A. Loda, and J. A. Earp. University of North Carolina at Chapel Hill.*
4. **An Analysis of Adolescent Suicide Attempts: A Validation of the Expendable Child Measure.** *J. Woznica and J. Shapiro. Division of Adolescent Medicine, Children's Hospital of Los Angeles, Calif.*
5. **Serious Sports Injuries in a Pediatric Emergency Department.** *G. Fleisher, N. Kuppermann, and J. Davis. Division of Emergency Medicine, Children's Hospital, Boston, Mass.*
6. **Unrecognized Pertussis in Adolescents.** *B. A. Cromer, J. Goydos, J. Hackell, J. Mezzatesta, C. Dekker, and E. A. Mortimer. Ohio State University, College of Medicine, Columbus; Children's Hospital, Columbus; Lederle Biologicals, Pearl River, NY; and Case Western Reserve University School of Medicine, Cleveland, Ohio.*
7. **Patterns of Middle School Health Room Use.** *J. C. Joost, L. S. Grossman, R. J. McCarter, and S. J. Verhulst. Division of Behavioral and Developmental Pediatrics, University of Maryland, Baltimore, and Baltimore County Board of Education.*
8. **Anticipatory Guidance for the Adolescent: Parental Concerns.** *R. M. Cavanaugh, M. Hastings-Tolsma, D. Keenan, and B. Buser. Department of Pediatrics, SUNY-Health Science Center, Syracuse.*

BEHAVIOR AND DEVELOPMENT

9. **Intraoral Sucrose Affects Prepubertal Children's Responses to Experimental Pain.** *A. R. Miller, R. G. Barr, and S. N. Young. The Montreal (Quebec) Children's Hospital, and Departments of Pediatrics and Psychiatry, McGill University, Montreal.*
10. **Bayley Infant Neurodevelopmental Screener (BINS) Prediction Profiles in Outcome of At-Risk Infants.** *G. P. Aylward, S. J. Verhulst, and S. Bell. Department of Pediatrics, Southern Illinois University School of Medicine, Springfield.*
11. **Outcome of Survivors Weighing $\leq$ 1000 Grams Using the World Health Organization (WHO) Classification.** *M. Peralta, K. G. Nelson, F. Gaudier, R. Goldenberg, M. Dubard, S. Johnson, and R. Steele. Department of Pediatrics, University of Alabama at Birmingham.*
12. **DDAVP and Enuresis: What Do We Know?** *M. E. K. Moffatt, S. Harlos, A. J. Kirshen, and L. Burd. Departments of Community Health Sciences and Pediatrics, University of Manitoba, Winnipeg.*
13. **Does Treatment of Constipation at a Young Age Prevent Constipation and Stool Soiling in the School-Aged Child.** *V. Loening-Baucke. Department of Pediatrics, University of Iowa, Iowa City.*
14. **Cranial Ultrasonography in Full-Term Cocaine-Exposed Infants.** *M. E. Montgomery, P. Montgomery, J. R. Ignacio, and V. James. Department of Pediatrics, The Children's Hospital of Buffalo, NY.*
15. **Evaluation of a Rapid Assay for Detection of Cocaine Metabolites in Urine Specimens.** *R. A. Belfer, B. L. Klein, D. A. Boenning, and S. J. Soldin. Emergency Medical Trauma Center, Washington, DC.*
16. **Randomized Controlled Clinical Trial of Three Interventions in the Management of Persistent Crying of Infancy.** *P. Parkin and C. Schwartz. Department of Pediatrics, The Hospital for Sick Children, Toronto, Ontario.*
17. **Left-Handedness as a Risk Factor for Accidental Trauma.** *C. J. Graham, R. Glenn, R. Dick, B. Allen, and J. Pasley. Department of Pediatrics, University of Arkansas and Arkansas Children's Hospital, Little Rock.*
18. **Athyrotic, Lingual and Goitrous Hypothyroid (HYPOT) Infants Exhibit Distinct Differences in Screening and Definitive Thyroid Tests: Implications for Misdiagnosis.** *D. R. MacMillan and C. C. Mabry. Departments of Pediatrics, University of Louisville (Ky) School of Medicine, and University of Kentucky School of Medicine, Lexington.*
19. **Hospitalization Of Children Born to Cocaine-Using Mothers.** *B. W. C. Forsyth, D. R. Wasserman, and J. M. Leventhal. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.*
20. **Which Children Grow in Response to Foster Care?***S. M. Horwitz, M. D. Simms, and J. D. Scinto. Department of Epidemiology and Public Health, Yale University, New Haven, Conn, and St Mary's Hospital, Waterbury, Conn.*
21. **Developmental Evaluation of Young Socially High-Risk Children: A Comparison of Three Screening Tests.** *B. P. Dreyer, C. D. Courtlandt, and A. H. Fierman. Department of Pediatrics, New York (NY) University School of Medicine.*
22. **Visual Reaction Time in Deaf and Hearing Children with Attention Deficit Disorders.** *D. P. Kelly, G. P. Aylward, M. L. Jones, S. J. Parker-Fisher, S. A. Bell, and S. J. Verhulst. Department of Pediatrics, Southern Illinois University School of Medicine, Springfield.*
23. **Uncertainty and Mental Health in Mothers of Children With Chronic Illnesses.** *K. Bencivenga, H. T. Ireys, and E. J. Silver. Preventive Intervention Research Center for Child Health, Department of Ambulatory Pediatrics, Albert Einstein College of Medicine, Bronx, NY.*
24. **Correlates of Elevated Stress Among Parents of Infants With Disabilities.** *J. Shonkoff, M. Krauss, C. Upshur, and P. Hauser-Cram. Department of Pediatrics, University of Massachusetts Medical School, Worcester.*
25. **Parent Protection Scale for Children Age 2-5 Years.** *M. Thomasgard, P. Metz, C. Edelbrock, and J. Shonkoff. Departments of Pediatrics and Psychiatry, University of Massachusetts Medical School, Worcester.*
26. **Relation Between Parental Overprotection and the Vulnerable Child Syndrome.** *M. Thomasgard, P. Metz, C. Edelbrock, and J. Shonkoff. Departments of Pediatrics and Psychiatry, University of Massachusetts Medical School, Worcester.*

27. **School Functioning of Very Low Birth Weight Children.** *P. K. Klebanov, J. Brooks-Gunn, and M. C. McCormick. Educational Testing Service, Princeton, NJ; Columbia University, New York, NY; and Harvard School of Public Health, Boston, Mass.*

CLINICAL ISSUES

28. **Coarctation of the Aorta: Failure of Early Detection in the Pediatric Patient.** *F. F. Ing, T. S. Starc, S. P. Griffiths, and W. M. Gersony. Division of Pediatric Cardiology, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, NY, and Babies Hospital, New York.*
29. **Respiratory Signs and Symptoms as Markers for Pneumonia in Febrile Infants Less Than Two Months of Age.** *D. Demestihas and A. E. Kornberg. Division of Emergency Medicine, The Children's Hospital of Buffalo, NY.*
30. **Predictors of Initial Glycemic Control in Newly Diagnosed Diabetic Children: A Randomized Trial.** *G. Dougherty, A. Schiffrin, D. White, and L. Ball. Departments of Pediatrics and Epidemiology and Biostatistics, McGill University, Montreal, Quebec, and Montreal Children's Hospital.*
31. **Reticulocyte Counts and Blood Smears in Jaundiced Infants.** *T. B. Newman, S. Hope, and L. Corash. Departments of Laboratory Medicine, Pediatrics, and Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco.*
32. **Are Well-Appearing Febrile Infants With Otitis Media at Risk for Serious Bacterial Illness?** *J. R. Avner, E. F. Crain, and M. D. Baker. Division of Ambulatory Pediatrics (Emergency Medicine), Albert Einstein College of Medicine, Bronx, NY, and Division of General Pediatrics/Emergency Medicine, Children's Hospital of Philadelphia, Pa.*
33. **When to Assess the Health of Children Entering Foster Care.** *R. Chernoff and T. Combs-Orme. Department of Pediatrics, University of Maryland, Baltimore; The Johns Hopkins University School of Medicine, Baltimore; and The Johns Hopkins School of Public Health and Hygiene.*
34. **Follow-up After Placing Tuberculin Skin Test: Which Method Is Best?** *K. J. Kemper. Department of Pediatrics, Harborview Medical Center, Seattle, Wash.*
35. **Failure of Standardized Respiratory Rate Measurement to Detect Pneumonia in Febrile Infants.** *J. A. Taylor, J. J. Batts, C. L. Talarico, E. W. Kouri, and W. P. Kerns. Departments of Pediatrics, Emergency Medicine, and Radiology, Carolinas Medical Center, Charlotte, NC.*
36. **Consumer Use of Tympanic Thermometry: Is It Reliable?** *D. T. Alexander and B. A. Kelly. Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, and Children's Hospital of Philadelphia.*
37. **Upper Urinary Tract Deterioration With Myelomeningocele.** *E. Charney, J. Melchionni, and H. Snyder III. Departments of Pediatrics and Surgery, University of Pennsylvania, Philadelphia, and Division of General Pediatrics and Urology, Children's Hospital of Philadelphia.*
38. **Tracheostomy Speaking Valves in the Pediatric Population: Experiences and Recommendations.** *U. Mehta and S. Albamonte. Children's Specialized Hospital, Mountainside, NJ.*
39. **The Immunization Status of Children With Spina Bifida.** *M. Raddish, D. A. Goldmann, L. C. Kaplan, and J. M. Perrin. Harvard Medical School, Boston, Mass; Massachusetts General Hospital, Boston; and Children's Hospital, Boston.*
40. **Aerosolized Epinephrine (AE) Use in the Treatment of Croup.** *N. C. Kunkel and M. D. Baker. Divisions of General Pediatrics and Emergency Medicine, Children's Hospital of Philadelphia, Pa.*
41. **Efficacy of a Herbal Tea Preparation in Infantile Colic.** *S. Alkrinawi, Z. Weizman, D. Goldfarb, and C. Bitran. Department of Pediatrics, Soroka Medical Center, Ben-Gurion University, Beer-Sheva, Israel.*
42. **Otitis Media: A Vulnerability Factor?** *M. Black and S. Sonnenschein. Department of Pediatrics, University of Maryland School of Medicine, Baltimore.*
43. **Single-Dose Ceftriaxone for the Treatment of Acute Otitis Media With Effusion.** *J. M. Chamberlain, D. W. Ochsenschlager, D. A. Boenning, and B. L. Klein. Emergency Medical Trauma Center, Washington, DC.*
44. **Asthma Claims from Children Receiving Medicaid/AFDC as a Basis for Selective HMO Enrollment.** *D. West, M. Stuart, A. Duggan, and C. DeAngelis. Department of Pediatrics, Alfred I. duPont Institute, Wilmington, Del; Maryland Department of Health and Mental Hygiene, Baltimore; and Department of Pediatrics, The Johns Hopkins University, Baltimore.*
45. **Tube Feedings Help.** *S. M. Naureckas and K. K. Christoffel. Department of Pediatrics, Northwestern University, Chicago, Ill, and Children's Memorial Hospital, Chicago.*
46. **Hepatitis B Screening of Indigent Mothers: Practical Aspects.** *V. A. Moyer. Department of Pediatrics, University of Texas Medical School and LBJ Hospital, Houston.*
47. **Infrequency of Adenotonsillar Hypertrophy (ATH) as a Proven Cause of Obstructive Sleep Apnea (OSA) in a Tertiary Care Children's Hospital.** *P. Dick, W. Feldman, A. Newman, and I. MacLuskey. Divisions of General Pediatrics and Respiratory Medicine, The Hospital for Sick Children, Toronto, Ontario.*
48. **The Reliability of Mid-Stream Urine Culture From Circumcised Male Infants Compared to Supra-Pubic Aspiration (SPA).** *J. Amir, M. Ginzburg, and I. Varsano. Department of Pediatrics, Hasharon Hospital, Petach Tikvah, Israel.*
49. **Yield From Stool Testing of Pediatric Inpatients.** *S. B. Meropol, A. A. Luberti, and A. R. De Jong. Department of Pediatrics, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pa.*

EMERGENCY MEDICINE AND CHILD ABUSE

50. **Preschool Aged Victims of Child Sexual Abuse.** *A. R. De Jong. Department of Pediatrics, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pa.*
51. **Child Sexual Abuse by Uncles.** *A. R. De Jong. Department of Pediatrics, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pa.*
52. **Prevalence and Recognition of Potential Growth Failure in a Pediatric Emergency Department.** *T. E. Hellmich, D. T. Wyatt, S. J. Jacobsen, and J. A. Gyuro. Department of Pediatrics, Medical College of Wisconsin, Milwaukee, and Children's Hospital of Wisconsin, Milwaukee.*
53. **Prehospital Management of Asthma Requiring Hospitalization.** *J. D. Fisher and R. J. Vinci. Department of Pediatric Emergency Medicine, Boston (Mass) City Hospital.*
54. **The Aftermath of Sexual Abuse (SA) Reporting.** *J. Lantos and W. Bass. Department of Pediatrics and Center for Clinical Medical Ethics, University of Chicago, Pritzker School of Medicine, and La Rabida Children's Hospital, Chicago, Ill.*
55. **Appropriate Use of Computed Tomography in the Emergency Room.** *J. M. Elser. Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, and Arkansas Children's Hospital, Little Rock.*
56. **A Follow-up Study of Behavior Problems Associated With Child Sexual Abuse.** *H. Dubowitz, M. Black, D. Harrington, and A. Verschoore. Department of Pediatrics, University of Maryland School of Medicine, Baltimore.*
57. **Sexual Abuse: Developmental Differences in Psychological Adjustment.** *M. Black, H. Dubowitz, and D. Harrington. Department of Pediatrics, University of Maryland School of Medicine, Baltimore.*
58. **Body Weight and Hymenal Opening Size in Prepubertal Suspected Sexual Abuse Victims.** *D. L. Kerns and M. L. Ritter. Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, Calif.*
59. **The Routine Use of Radiography and Arterial Blood Gases (ABGS) in the Evaluation of Blunt Trauma (BT) in Children.** *S. Kharasch, R. Vinci, and E. Hirsch. Departments of Pediatrics and Surgery, Boston (Mass) City Hospital.*
60. **Parents' Understanding of Their Child's Diagnosis After a Visit to the Emergency Department.** *G. Berera, C. Berkowitz, and R. Lewis. Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, Calif.*
61. **The Potential Impact of Using an Urban Emergency Department (ED) to Immunize Pre-School Children.** *L. M. Bell and N. I. Lopez. Emergency Medicine, Division of General Pediatrics, Children's Hospital of Philadelphia, Pa, and University of Pennsylvania, Philadelphia.*
62. **The Efficacy of Parent Education in the Pediatric Emergency Department.** *V. A. Almeida, S. E. Krug, and T. S. Yamashita. Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio, and Rainbow Babies and Children's Hospital, Cleveland.*

63. **Factors Associated With Non-Medical Admissions of Children From the Emergency Department.** *S. Krug, R. Paul, J. Chessare, N. Christopher, L. Satkowiak, and T. Yamashito. Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio, and Rainbow Babies and Children's Hospital, Cleveland.*
64. **The Incidence of Acute Infections in HIV Positive Children Presenting to the Emergency Department.** *M. B. Harper, H. M. Pinkert, and G. R. Fleisher. Department of Medicine, Divisions of Emergency Medicine and Infectious Disease, Children's Hospital, Boston, Mass.*
65. **Application of Minimum Threshold Criteria for Reporting Child Abuse From Health Care Settings.** *J. E. Paradise and S. Forman. Department of Pediatrics, Boston (Mass) University School of Medicine, and Boston City Hospital.*
66. **Gunshot Wounds in an Urban Children's Hospital.** *D. Hamburger, C. DiGuiseppi, C. Gotschall, J. Wright, D. Boenning, and M. Eichelberger. Emergency Trauma Services, Children's National Medical Center, Washington, DC.*
67. **Efficacy of Magnesium Citrate in Pediatric Ingestions.** *Y. Sue, M. Shannon, and A. Woolf. Department of Medicine, Children's Hospital, Boston, Mass.*
68. **Decreasing Inappropriate ED Use.** *L. Grossman, L. Fisher, C. Lancaster, A. Dietrich, and W. Cotton. Department of Pediatrics, Children's Hospital, Columbus, Ohio, and Ohio State University, College of Medicine, Columbus.*
69. **Decision Rules for Predicting Undervaccination of Preschool-Age Emergency Department Patients.** *S. G. Humiston, L. E. Rodewald, P. G. Szilagyi, R. F. Raubertas, K. J. Roghman, L. A. Cove, C. B. Doane, and C. B. Hall. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry, Strong Memorial Hospital, Rochester.*

EPIDEMIOLOGY AND PREVENTION

70. **Immunization Status and Birth Order.** *S. J. Schaffer and P. G. Szilagyi. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*
71. **A Population at Risk: Children in Foster Care.** *M. A. Szilagyi, P. G. Szilagyi, T. Webb, and H. Ghanizadeh. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*
72. **Injuries to Children Involving Home Exercise Equipment.** *J. H. Gould and A. R. De Jong. Department of Pediatrics, Thomas Jefferson University Hospital, Philadelphia, Pa.*
73. **Illness Severity and Adjustment.** *E. C. Perrin, C. C. Ayoub, and J. B. Willett. Harvard Graduate School of Education, Cambridge, Mass, and University of Massachusetts Medical Center, Worcester.*
74. **Screening for Childhood Lead Poisoning: A Decision Analysis.** *D. Glotzer, H. Bauchner, and K. A. Freedberg. Departments of Pediatrics and Medicine, Boston (Mass) University School of Medicine, and Boston City Hospital.*
75. **Majority of Children in an Inner-City Clinic Population Have Lead Levels Exceeding the Center for Disease Control Revised Intervention Threshold.** *S. T. Melman, D. Christiansen, and M. D. Schorr. Department of Pediatrics, Hahnemann University Hospital, Philadelphia, Pa.*
76. **Health Status of Children of Cambodian Refugees.** *C. J. Homer, H. Egan, M. K. Smith, and J. Ware. Harvard University, Boston, Mass.*
77. **Lead Screening Opportunities Missed Among Urban Children.** *J. R. Campbell, M. Weitzman, and K. McConnochie. Department of Pediatrics, University of Rochester, NY.*
78. **Epidemiology of Injuries in Children From Electrically Operated Garage Doors.** *U. Sankrithi and D. Tiedeman. Department of Pediatrics, University of Washington, Seattle, and Children's Hospital and Medical Center, Seattle.*
79. **Zapping A Myth: How Safe Are Microwave Ovens?** *E. C. Powell and R. R. Tanz. Department of Pediatrics, Children's Memorial Hospital, Chicago, Ill, and Northwestern University, Chicago.*
80. **Does Home Abatement Lower Blood Lead Levels in Children With Class II Lead Poisoning?** *S. Swindell and E. Charney. Department of Pediatrics, University of Massachusetts Medical Center, Worcester.*
81. **Childhood Asthma and Poverty: Prevalence, Impact, and Health Services Utilization.** *N. Halfon and P. W. Newacheck. Center for the Vulnerable Child, Children's Hospital, Oakland, Calif; Institute for Health Policy Studies, School of Medicine, University of California, San Francisco; and the Department of Community Health Sciences, School of Public Health, and Department of Pediatrics, School of Medicine, UCLA.*
82. **Epilepsy as a Risk Factor for Submersion Injury in Children.** *D. S. Diekema, L. Quan, and V. L. Holt. Department of Emergency Services, Children's Hospital and Medical Center, Seattle, Wash, and the Department of Health Services, University of Washington, Seattle.*
83. **Lead Poisoning in a Non-Inner City Practice.** *D. B. Nelson, J. M. Cox, D. Richmond, M. Toporowicz, and A. Zuckerman. Department of Pediatrics, Georgetown University Children's Medical Center, Washington, DC.*
84. **A Profile of Burn Injuries in an Urban Primary Care Population.** *L. Banco, L. Remington, G. Lapidus, and M. Braddock. Department of Pediatrics, Hartford (Conn) Hospital.*
85. **Effectiveness of a School Based Education Program in Increasing Bicycle Helmet Use and Awareness in School Aged Children.** *P. Parkin, L. Spence, X. Hu, and D. Wesson. Departments of Pediatrics and Surgery, The Hospital for Sick Children, Toronto, Ontario.*
86. **Taxicabs and Child Restraint.** *R. S. Walter and A. Kuo. Department of Pediatrics, Alfred I. duPont Institute, Wilmington, Del, and University of Maryland, Baltimore.*
87. **Prevalence of Substance Abuse Among Pregnant Women in Utah.** *K. F. Buchi, R. A. Chase, and M. W. Varner. Departments of Pediatrics and Obstetrics-Gynecology, University of Utah School of Medicine, Salt Lake City.*
88. **Prior Risk Status of Postneonatal Deaths: A Total Population Study.** *A. Kempe, P. H. Wise, H. Rinehardt, and N. S. Wampler. Department of Medicine, Children's Hospital, Boston.*

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

89. **Student Clinical Experience and Exam Performance: Are They Related?** *L. W. Greenberg and P. Getson. Department of Pediatrics, George Washington University School of Medicine, and Children's National Medical Center, Washington, DC.*
90. **Evening Appointment Reminder Calling Minimizes Patient 'No Shows' (PNS) and Saves Money.** *W. Primack, D. Henderson, and T. Hendershott. Fallon Clinic and Fallon Community Health Plan, Worcester, Mass.*
91. **Changes in Diet and Parents' Health Perceptions One Year after Pediatric Cholesterol Screening.** *C. M. Lannon and J. A. Earp. Departments of Pediatrics and Health Behavior, University of North Carolina at Chapel Hill.*
92. **Enhancing Otoscopic Skill of Pediatric Residents.** *A. Hoberman and P. H. Kaleida. School of Medicine, University of Pittsburgh, Pa, Department of Pediatrics, Children's Hospital of Pittsburgh.*
93. **Pediatric Residents Improve Well Child Examinations During a Six Month Training Experience.** *D. P. McCormick and G. M. Rassin. Department of Pediatrics, University of Texas Medical Branch, Galveston.*
94. **Physician Interview Style and Maternal Disclosure of the Use of Corporal Punishment.** *L. S. Wissow, M. E. H. Wilson, and D. Roter. Department of Pediatrics, School of Medicine, and Department of Health, Policy, and Management, School of Hygiene, the Johns Hopkins Institutions, Baltimore, Md.*
95. **A Comparison of Resident and Faculty Learning Styles and Implications for Teaching.** *E. Kosower and N. Berman. Harbor-UCLA Medical Center, UCLA School of Medicine, Torrance.*
96. **Home Availability of Ipecac: Our Actions Speak Louder than our Words.** *P. L. Townsend, H. Binns, and R. R. Tanz. Department of Pediatrics, Children's Memorial Hospital, Chicago, Ill, and Northwestern University Medical School, Chicago.*
97. **Pediatric Education in Emergency Medicine Residency Programs: Ten Years Later.** *S. P. Ros, F. Cetta, and S. Ludwig. Department of Pediatrics, Loyola University Medical Center, Maywood, Ill.*
98. **Maternal Identification of Persistent Suppurative Otitis in Young Children.** *A. L. Olson and S. W. Kairys. Department of Maternal and Child Health, Dartmouth Medical School, Hanover, NH.*

Wednesday, May 6
9 AM-NOON

CLINICAL ISSUES

Room 308 Convention Center

Moderators: *Thomas G. DeWitt, MD, and James Seidel, MD, PhD*

9:00 **The Utility of the Urinalysis (UA) in Making a Presumptive Diagnosis of Urinary Tract Infection (UTI) in Children.** *J. A. Lohr, M. G. Portilla, T. G. Geuder, M. L. Dunn, and S. M. Dudley. Departments of Pediatrics, University of North Carolina at Chapel Hill, and University of Virginia, Charlottesville.*

9:15 **Preferences for Short Term and Permanent Clinical Outcomes.** *S. M. Downs and R. A. McNutt. Departments of Pediatrics and Medicine, University of North Carolina at Chapel Hill.*

9:30 **Efficacy of the Young Infant Observation Scale (YIOS) in Correlating Clinical Appearance With Infectious Outcome in Febrile Young Infants.** *W. A. Bonadio, H. Hennes, D. Smith, R. Ruffing, M. Melzer-Lange, P. Lye, and D. Isaacman. Department of Pediatrics, Medical College of Wisconsin, Milwaukee.*

9:45 **Cow Milk Formula vs Soy-Based Formula After Acute Diarrhea: A Randomized Controlled Trial.** *U. Allen, K. McLeod, and E. Wang. Division of Pediatric Infectious Disease, The Hospital for Sick Children, Toronto, Ontario.*

10:00 **Prospective Evaluation of Complications of Local Anesthesia for Neonatal Circumcision.** *L. W. Snellman and H. J. Stang. Department of Pediatrics and Adolescent Medicine, Group Health Inc, White Bear Lake, Minn.*

10:15 **Streptococcal Pharyngitis in Young Children.** *J. Amir, Y. Shecter, N. Eilam, and I. Varsano. Department of Pediatrics, Hasharon Hospital, Petach Tikvah, Israel.*

10:30 **Breast Feeding and Recurrent Otitis Media in the First Year of Life.** *B. Duncan, J. Ey, C. Holberg, A. Wright, F. Martinez, and L. Taussig. Respiration Science Center, Department of Pediatrics, Steele Memorial Children's Research Center, University of Arizona, Tucson.*

10:45 **Dimercaptosuccubate (DMSA) as Chelation Agent for Children With Low Level Lead Toxicity: An Open Pilot Trial.** *E. S. Stremski, G. C. Fifield, and M. A. Jagodzinski. Department of Pediatrics, Hennepin County Medical Center, Minneapolis, Minn.*

11:00 **Severity of Lower Respiratory Illnesses (LRIs) in Infants: Prediction at Presentation.** *L. C. Garfunkel and K. M. McConnochie. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry, and Rochester General Hospital.*

11:15 **Management of Febrile Infants (FI) 15 to 28 Days of Age With Intramuscular (IM) Ceftriaxone (CTX) and One Day of Inpatient Observation.** *M. N. Baskin, E. J. O'Rourke, and G. R. Fleisher. Department of Pediatrics, Harvard Medical School, Boston, Mass, and Children's Hospital, Boston.*

11:30 **Reevaluation of Criteria to Identify Infants Evaluated for Possible Sepsis (PS) at Low Risk (LR) for Serious Bacterial Infection (SBI).** *J. A. Jaskiewicz, C. A. McCarthy, A. C. Richardson, and K. R. Powell. Department of Pediatrics, University of Rochester (NY) Medical Center.*

11:45 **Septic Arthritis (SAH) Versus Transient Synovitis (TSH) of HIP: The Value of Screening Labs.** *M. A. Del Beccaro, A. N. Champoux, and P. M. Mendelman. Department of Pediatrics, University of Washington, Seattle, and Children's Hospital and Medical Center, Seattle.*

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Room 301/303 Convention Center

Moderators: *Judith S. Palfrey, MD, and*
John M. Pascoe, MD, MPH

9:00 **Maternal Rating of Child Health at School Age for VLBW Children: Persistence of the Vulnerable Child Syndrome.** *M. C. McCormick, K. Workman, and J. Brooks-Gunn. Department of Maternal and Child Health, and Joint Program in Neonatology, Harvard University, Boston, Mass, and Teachers College, Columbia University, New York, NY.*

9:15 **Beneficial Behavioral Effects of Successful Encopresis Therapy.** *T. Nolan, C. Coffey, F. Oberklaid, and L. Bond. Departments of Pediatrics and Ambulatory Pediatrics, University of Melbourne, Australia, and Royal Children's Hospital, Melbourne.*

9:30 **Pediatricians' Approaches to Developmental Problems: 15 Years Later.** *A. E. Dobos, P. H. Dworkin, and B. Bernstein. Department of Pediatrics, University of Connecticut Health Center, Farmington.*

9:45 **The Usefulness of the Battelle Developmental Inventory Screening Test.** *F. P. Glascoe, K. E. Byrne, and A. G. Westbrook. Department of Pediatrics, Child Development Center, Vanderbilt University, Nashville, Tenn.*

10:00 **Family Factors Influence Psychosocial Diagnoses.** *S. M. Horwitz, J. M. Leventhal, and P. J. Leaf. Departments of Epidemiology and Public Health and Pediatrics, Yale University, New Haven, Conn.*

10:15 **Pediatric Clinical Assessment of Mother Child Interaction: Concurrent and Predictive Validity.** *P. Casey, R. Bradley, K. Barrett, and D. Spiker. Department of Pediatrics, University of Arkansas, and Arkansas Children's Hospital, Little Rock.*

10:30 **Communicating Medical Bad News: Parent Preferences and Experiences.** *M. C. Sharp, R. P. Strauss, and S. C. Lorch. Departments of Pediatrics, Social Medicine, and Dental Ecology, University of North Carolina at Chapel Hill.*

10:45 **Resident Response to Psychosocial Issues.** *R. K. Kamei, L. O. Murphy, and R. H. Pantell. Department of General Pediatrics, University of California, San Francisco.*

11:00 **Mother-Child Interaction and the Development of Infants With Disabilities.** *J. Shonkoff, P. Hauser-Cram, C. Upshur, and M. Krauss. Department of Pediatrics, University of Massachusetts Medical School, Worcester.*

11:15 **Screening Mothers of Young Children for Substance Abuse.** *K. J. Kemper and T. Babonis. Department of Pediatrics, Harborview Medical Center, Seattle, Wash.*

11:30 **Clinical Preventive Service Efficacy and Adolescents' Risky Behaviors.** *S. M. Downs and J. D. Klein. Department of Pediatrics, University of North Carolina at Chapel Hill.*

11:45 **Correlates of Mental Health of Caregivers of Severely Ill Children.** *J. M. Perrin, S. R. Bloom, M. Raddish, J. Natkins, and S. L. Gortmaker. Department of Pediatrics, Massachusetts General Hospital, Boston, and Harvard Medical School and School of Public Health, Boston.*

EMERGENCY MEDICINE AND CHILD ABUSE

Room 309 Convention Center

Moderators: *Carol Berkowitz, MD and Stephen Ludwig, MD*

9:00 **Contact Burn Injuries Among Children in an Urban Emergency Department.** *L. Banco, G. Lapidus, and M. Braddock. Department of Pediatrics, Hartford (Conn) Hospital.*

9:15 **Vaginal Discharge as a Marker of Gonorrhea in Pre-Pubertal Females.** *R. A. Shapiro, C. J. Schubert, and P. Myers. Division of Emergency Medicine, Children's Hospital Medical Center, Cincinnati, Ohio.*

9:30 **Reproducibility of Field Prognostic Indicators in Pediatric Submersion Victims Receiving Prehospital Care.** *L. Quan and D. Kinder. Department of Pediatrics, University of Washington Medical School, Seattle.*

9:45 **The Impact of Criminal Courts on Sexually Abused Children.** *D. K. Runyan, W. M. Hunter, M. D. Everson, and D. Whitcomb. Department of Social Medicine, University of North Carolina at Chapel Hill.*

10:00 **Understanding Fatal Child Abuse.** *R. A. Hicks and D. C. Gaughan. Department of Pediatrics, Wright State University, and The Children's Medical Center, Dayton, Ohio.*

10:15 **Exposure to Violence Among Inner City Parents and Young Children.** *L. Taylor, V. Harik, and B. Zuckerman. Division of Developmental and Behavioral Pediatrics, Boston (Mass) City Hospital, and School of Public Health, Boston University School of Medicine.*

10:30 **Adolescents Trying to Conceive: An Association with Child Sexual Abuse?** *D. Y. Rainey, C. Stevens-Simon, and D. W. Kaplan. Departments of Pediatrics, Wake Forest University, Winston-Salem, NC, and University of Colorado Health Science Center, Denver.*

10:45 **An Emergency Department Trial of Continuously vs. Intermittently Nebulized Albuterol.** *D. Steele and M. D. Baker. Divisions of General Pediatrics and Emergency Medicine, Children's Hospital of Philadelphia, Pa.*

11:00 **The Successful Use of a Metal Detector in Locating Coins Ingested by Children.** *S. P. Ros and F. Cetta. Department of Pediatrics, Loyola University Medical Center, Maywood, Ill.*

11:15 **Utility of Routine Laboratory Testing in the Pediatric Trauma Patient.** *D. J. Isaacman, R. J. Scarfone, and S. I. Kost. Department of Pediatrics, University of Pittsburgh (Pa) School of Medicine, and Children's Hospital of Pittsburgh.*

11:30 **Violence in the Pediatric Emergency Department (PED).** *C. M. McAneney and K. N. Shaw. Divisions of Emergency Medicine, Children's Hospital of Cincinnati, Ohio, and Children's Hospital of Philadelphia, Pa.*

11:45 **Access to Care for Children Visiting the Emergency Room (ER) With Acute Exacerbations of Asthma.** *A. E. Davidson, D. E. Klein, G. A. Settipone, and A. J. Alario. Departments of Ambulatory Pediatrics and Allergy, Rhode Island Hospital, Providence.*

GENERAL PEDIATRICS

Room 310 Convention Center

Moderators: *Sandra Elvik-Jacobson, MS, CPNP, and Lucy Osborn, MD*

9:00 **An Analysis of Group Versus Individual Health Supervision Visits.** *R. L. Rice, C. E. Miles, and C. J. Slater. Department of Pediatrics, University of Wisconsin, Madison.*

9:15 **Children Without Health Insurance: Prior Coverage and Expectations for Future Coverage.** *J. L. Holl, P. G. Szilagyi, L. E. Rodewald, L. R. Pollard, and J. Halligan. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*

9:30 **A Successful Randomized Control Trial to Increase the Use of Cloth Diapers.** *M. Sutton, H. Bauchner, and J. Howland. Departments of Pediatrics and Public Health, Boston (Mass) City Hospital, and Boston University School of Medicine.*

9:45 **Career Choices and Satisfaction: A Comparison Between Practitioners and Academicians.** *L. W. Greenberg, M. F. Guagliardo, P. Getson, L. S. Jewett, and M. S. Wolf. Department of Pediatrics, The George Washington University School of Medicine, and Children's National Medical Center, Washington, DC.*

10:00 **Improving Access to Services for the Poor.** *W. Bithoney, S. Corso, R. Lauerman, and J. Bigby. Division of General Pediatrics, Children's Hospital, Boston, Mass.*

10:15 **Clinical Characteristics of Children Proposed to Receive Tympanostomy Tubes.** *L. C. Kleinman, J. Kosecoff, R. W. DuBois, and R. H. Brook. UCLA Clinical Scholars Program.*

10:30 **Prevalence of Viral Pathogens on Fomites in Day Care Facilities.** *A. Butz, P. Fosarelli, J. Dick, and R. Yolken. School of Nursing and Department of Pediatrics, The Johns Hopkins University, Baltimore, Md.*

10:45 **What is the Cost of Health Care for Foster Children?** *J. I. Takayama, A. B. Bergman, and F. A. Connell. Department of Pediatrics and School of Public Health and Community Medicine, University of Washington, Seattle.*

11:00 **Self-Medication in Childhood: Experience at Summer Camp.** *M. C. Rudolf, B. Youth, S. Riggs, and A. J. Alario. Department of Pediatrics, Rhode Island Hospital-Brown University School of Medicine, Providence.*

11:15 **Factors Affecting Pediatricians' Participation in Medicaid in North Carolina.** *P. A. Margolis, R. L. Cook, J. A. Earp, C. M. Lannon, L. L. Keyes, and J. D. Klein. Department of Pediatrics, University of North Carolina at Chapel Hill.*

11:30 **Understanding of AIDS by Elementary School Children: A Developmental Survey.** *D. Schonfeld, S. Johnson, E. Perrin, L. O'Hare, and D. Cicchetti. Department of Pediatrics and Child Study Center, Yale University School of Medicine, New Haven, Conn; University of California, San Francisco; and University of Massachusetts, Worcester.*

11:45 **The Pediatrician's Private Office as an Ambulatory Placement in a Clerkship Rotation: Physicians' Opinions of the Learning Experience.** *R. Schneider, D. H. Shawn, and D. Cleave-Hogg. Department of Pediatrics, University of Toronto, Ontario.*

PREVENTION AND EPIDEMIOLOGY

Room 307 Convention Center

Moderators: *Ruth T. Gross, MD, and John M. Leventhal, MD*

9:00 **Prevalence of Lead Exposure in a Clinic Utilizing 1991 Center for Disease Control (CDC) Recommendations.** *S. D. Blatt, H. L. Weinberger, and B. Helu. Department of Pediatrics, School of Medicine, SUNY Health Science Center, Syracuse.*

9:15 **Influence of Circumcision Status on Urinary Tract Infections in Pediatric Males.** *H. J. Stang, L. W. Snellman, and J. M. Stang. Department of Pediatrics, Group Health Inc, White Bear Lake, Minn.*

9:30 **Injury Prevention Training and Knowledge Among Urban Poor.** *G. L. Foltin, B. P. Dreyer, J. Comis, Jr., J. Fine, A. H. Fierman, and M. Wren. Department of Pediatrics, New York University School of Medicine.*

9:45 **Universal Urine Toxicologic Screening in an Urban Nursery.** *P. T. Horn, J. Mendelsohn, M. I. Bowers, M. Chappen, J. R. Schreier, S. H. Spalding, J. Weyher, and J. E. Berkelhamer. Department of Pediatrics, University of Chicago, Ill.*

10:00 **Profile of Uninsured Children in the United States: Lessons from the 1988 National Health Interview Survey-Child Health Supplement (1988 NHIS-CHS).** *J. L. Holl, P. G. Szilagyi, L. E. Rodewald, K. J. Roghmann, and M. Weitzman. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.*

10:15 **Maternal Smoking Patterns and Risk of SIDS.** *K. C. Schoendorf. Division of Analysis, National Center for Health Statistics, Hyattsville, Md.*

10:30 **Pediatric Injury Mortality and Morbidity: Canadian and American Experience 1965-1987.** *M. Hodge, G. Dougherty, and B. Pless. Departments of Pediatrics and Epidemiology and Biostatistics, McGill University, Montreal, Quebec, and Montreal Children's Hospital.*

10:45 **Television Viewing, Obesity and Physical Activity Among Adolescent Females: Cross-Sectional and Longitudinal Analyses.** *T. N. Robinson, L. D. Hammer, J. D. Killen, C. B. Taylor, H. C. Kraemer, D. M. Wilson, and C. Hayward. Stanford University School of Medicine, Palo Alto, Calif.*

11:00 **Stressful Life Events and Pediatric Medical Visits.** *K. W. Bruno, S. M. Horwitz, and P. J. Leaf. Department of Epidemiology and Public Health, Yale University, New Haven, Conn.*

11:15 **Helmets! All the Pros Wear Them.** *M. S. Puczynski, T. G. Chakurda, D. A. Marshall, and J. M. Lynch. Allegheny General Hospital, Medical College of Pennsylvania, Pittsburgh.*

11:30 **Breastfeeding Promotion in Public Health Clinics.** *B. A. DeFrancesco, P. R. Wood, P. R. Villarreal and N. Schweers. University of Texas Health Science Center, San Antonio.*

11:45 **Risk Factors Associated with Malnutrition in Children Under Five (5) in the Mazowe District of Zimbabwe.** *B. Z. Radebe. Department of Pediatrics and Child Health, University of Zimbabwe (APA International Health Research Award Winner, 1992).*

APA Debate

Wednesday, May 6
8:30 PM-10:00 PM

Constellation Ballroom A
Hyatt Hotel

Resolved: That the proliferation of subspecialties is not in the best interest of general pediatrics.

Moderator: *Kathleen G. Nelson, MD, APA President;*
Professor of Pediatrics; and
Director, Division of General Pediatrics,
Children's Hospital, Birmingham, Ala

Pro Resolution: *Joel J. Alpert, MD,* Professor and Chairman, Department of Pediatrics, Boston City Hospital and Boston University School of Medicine.
Russell W. Chesney, MD, Le Bonheur Professor and Chairman, Department of Pediatrics, University of Tennessee, College of Medicine, Memphis, and Vice President of Academic Affairs, Le Bonheur Children's Medical Center.

Con Resolution: *Elizabeth R. McAnarney, MD,* Professor of Pediatrics, Associate Chairman for Academic Affairs, Chief, Division of Adolescent Medicine, Rochester University Medical School.
Michael A. Simmons, MD, Professor and Chairman, Department of Pediatrics, University of Utah School of Medicine, and Medical Director, Primary Children's Medical Center.

APA General Plenary Session

Thursday, May 7
8:00 AM-12:30 PM

Room 309
Convention Center

Moderator: *Modena E. H. Wilson, MD, MPH*

8:00 **Correcting Respiratory Rate (RR) for the Presence of Fever.** *A. M. Gadomski. Division of General Pediatrics, University of Maryland, Baltimore.*

8:15 **Intergenerational Patterns of Child Abuse: Do Girls Who Were Abused Grow Up to Maltreat Their Children?** *S. E. Dobbs and J. M. Leventhal. Department of Pediatrics, Yale University School of Medicine and Yale-New Haven (Conn) Hospital.*

8:30 **Peak Serum Bilirubin in Normal-Sized Infants and Neurodevelopmental Outcome at Age 7: A Closer Look at the Collaborative Perinatal Study.** *T. B. Newman and M. Klebanoff. Departments of Laboratory Medicine, Pediatrics, and Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, and National Institute of Child Health and Development, Bethesda, Md.*

8:45 **The Role of School Policies in Deterring Adolescent Tobacco Use.** *J. C. Pederson. Department of Pediatrics, University of Washington, Seattle.*

9:00 **The Relationship of Temperament and Parent Expectations to Child Coping During Medical Procedures.** *K. A. Merritt and K. M. Gil. Department of Pediatrics, Duke University Medical Center, Durham, NC.*

9:15 **Non-Financial Barriers to Care.** *C. M. Lannon, P. A. Margolis, and J. A. Earp. Departments of Pediatrics and Health Behavior, University of North Carolina at Chapel Hill.*

9:30 **PRESIDENT'S ADDRESS.** *Kathleen G. Nelson, MD*

10:00 **INTERMISSION**

10:15 **Medical Findings in Child Sexual Abuse Cases With Perpetrator Confessions.** *D. L. Kerns and M. L. Ritter. Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, Calif.*

10:30 **Infant Health Care Utilization Predicted by Prenatal Care.** *A. Butz, L. Caleb, and B. Rosenstein. Department of Pediatrics and School of Nursing, The Johns Hopkins University, Baltimore, Md.*

10:45 **Intranasal Midazolam as an Adjunct to Suturing Small Children.** *D. West, M. Theroux, D. Corrdry, P. Hyde, K. Cronan, R. Kettrick, and S. Bachrach. Departments of Pediatrics and Anesthesiology, Alfred I. duPont Institute, Wilmington, Del.*

11:00 **Recent Trends in the Prevalence and Impact of Childhood Asthma.** *S. Gortmaker, M. Weitzman, J. Perrin, and A. Sobol. Harvard University School of Public Health, Boston, Mass, and University of Rochester (NY) School of Medicine and Dentistry.*

11:15 **Neonatal Outcome in Infants With Evidence of Fetal Exposure to Opiates, Cocaine and Cannabinoids.** *P. Nair and S. Rothblum. Department of Pediatrics, University of Maryland School of Medicine, Baltimore.*

11:30 **A Comparison of the Development of Homeless and Domiciled Poor Children.** *C. D. Courtlandt, B. P. Dreyer, A. H. Fierman, G. Benincasa, and J. Rivera. Department of Pediatrics, New York (NY) University School of Medicine.*

11:45 **INTERMISSION**

12:00 **ARMSTRONG LECTURE.** *Children's Television Workshop, David V. B. Britt*

2:00 PM - 5:00 PM
APA Special Interest Groups
(See page 442)
APA Workshops
(See page 442)

Annual Meeting
The American Pediatric Society and
The Society for Pediatric Research

Baltimore Convention Center

Monday, May 4	Tuesday, May 5	Wednesday, May 6	Thursday, May 7
	8:00 AM-11:30 AM APS PLENARY SESSION: APS Presidential Address; APS Presidential State-of-the-Art Symposium *Genetics is the Science & Medicine of the Future*	**8:00AM-10 AM** SPR PLENARY SESSION; SPR Presidential Address; Young Investigator Award; Richard D. Rowe Award; Medical Student, House Officer, and Fellow Awards	**8:00 AM-11:30 AM** APS/SPR Subspecialty Platform Sessions IV
	12:30 PM-1:30 PM APS John Howland Award and Joseph W. St Geme, Jr, Leadership Award	**8:30 AM-2:00 PM** APS/SPR/APA Exhibits **9:30 AM-12:00 PM** APS/SPR Poster Session II* **10:00 AM-12:30 PM** APS/SPR Poster Symposia	**11:00 AM-4:00 PM** APS/SPR/APA Exhibits SPR Business Meeting
1:00 PM-4:00 PM Joint Subspecialty Platform Sessions with AAP/ASCI/AFCR, Hematology/Oncology Renal & Electrolytes **1:00 PM-4:00 PM** Joint Featured Research Symposia with AAP/ASCI/AFCR, *AIDS and Retroviral Diseases;* *Cytokines, Interleukins and their Receptors;* *Genetic Basis of Disease;* *Growth Factors, Growth and Differentiation* **4:00 PM-6:00 PM** Joint Poster Session* with AAP/ASCI/AFCR **6:30 PM-10:00 PM** APS/SPR Subspecialty Platform Sessions I	**1:30 PM-5:00 PM** APS/SPR Subspecialty Platform Sessions II **1:30 PM-5:00 PM** APS/SPR/APA Joint Subspecialty Platform Sessions **5:00 PM-9:00 PM** APS/SPR/APA Poster Session I* **5:00 PM-9:00 PM** APS/SPR/APA Exhibits **5:30 PM-8:00 PM** APS/SPR Poster Symposia **8:00 PM-9:00 PM** APS/SPR/APA Opening Reception *(All Attendees Welcome)*	**12:30 PM.-1:45 PM** APS Business Meeting **2:00 PM-5:30 PM** SPR PLENARY SESSION; SPR Presidential State-of-the-Art Symposium, *Advances in Developmental Biology: Implications for the Future of Pediatric Research* **2:00 PM-5:30 PM** APS/SPR Subspecialty Platform Sessions III	**1:00 PM.-4:00 PM** APS/SPR Poster Session* **1:30 PM.-4:00 PM.** APS/SPR Poster Symposia

*Refer to pocket program for author attendance schedule

The American Pediatric Society and the Society for Pediatric Research
1992 – Subspecialty Platform Session Schedule

Monday, May 4 6:30 PM-10:00 PM	Tuesday, May 5 1:30 PM-5:00 PM	Wednesday, May 6 2:00 PM-5:30 PM	Thursday, May 7 8:00 AM-11:30 AM
Clinical Bioethics *(Rooms 301/303/305)*	Adolescent Medicine *(Room 308)*	Critical Care *(Room 308)*	Cardiology *(Room 308)*
Genetics *(Room 309)*	Behavioral Pediatrics *(Room 309)*	Developmental Pharmacology I *(Rooms 319/321/323)*	Developmental Biology II *(Rooms 101/103)*
Hematology/Oncology I *(Rooms 319/321/323)*	Dysmorphology & Teratology *(Rooms 319/321/323)*	Developmental Biology I *(Rooms 101/103)*	Developmental Pharmacology II *(Rooms 106/108)*
Infectious Diseases I *(Room 317)*	Epidemiology & Preventive Pediatrics *(Room 317)*	Endocrinology I *(Rooms 105/107)*	Endocrinology II *(Rooms 105/107)*
Metabolism & Diabetes I *(Room 310)*	Gastroenterology & Nutrition I *(Room 307)*	Gastroenterology & Nutrition II *(Room 307)*	Genetics II *(Rooms 319/321/323)*
Neonatology – General I *(Hall A)*	General Pediatrics & Pediatric Education *(Room 310)*	Infectious Diseases II *(Room 317)*	Immunology II *(Room 307)*
Nephrology I *(Room 308)*	Immunology I *(Rooms 101/103)*	Neonatal Cardiology *(Rooms 319/321)*	Hematology/Oncology II *(Rooms 301/303/305)*
Pulmonology I *(Room 307)*	Metabolism & Diabetes II *(Rooms 106/108)*	Neonatal Epidemiology & Follow-up *(Room 309)*	Neonatal Infectious Diseases *(Room 310)*
	Neonatology – General II *(Hall A)*	Neonatal Immunology & Hematology *(Rooms 301/303)*	Neonatal Nutrition & Metabolism *(Room 317)*
	Nephrology II *(Rooms 301/303/305)*	Pulmonology II *(Room 310)*	Neonatal Pulmonology *(Hall A)*
	Neurology *(Rooms 105/107)*		

1992 APS/SPR/APA Exhibitors

EXHIBITING COMPANY	CITY, STATE	BOOTH NUMBER
Ackrad Laboratories	Cranford, NJ	433
Air-Shields Vickers	Hatboro, Pa	200
Airborne Life Support Systems	Austin, Tex	521
Allscrips Pharmaceuticals	Vernon Hills, Ill	409
Baker Cummins Pharmaceuticals Inc	Miami, Fla	351
Bear Medical Systems Inc	Riverside, Calif	307
Bicore Monitoring Systems	Irvine, Calif	401
Bird Products Corporation	Riverside, Calif	238
Bunnell Incorporated	Salt Lake City, Utah	501
Burroughs Wellcome Company	Research Triangle Park, NC	424
CHECKOUT Software Systems	Muncie, Ind	304
Children's Hospital & Medical Center of Cincinnati	Cincinnati, Ohio	513
CNS Inc	Chanhassen, Minn	427
Colgate-Hoyt Laboratories	Canton, Mass	232
Consolidated Products & Services	North Quincy, Mass	311
Contemporary Pediatrics	Montvale, NJ	441
Cook Critical Care	Bloomington, Ind	104
Corometrics Medical Systems Inc	Wallingford, Conn	418, 420
Coulter Corporation	Hialeah, Fla	432
Ebsco Reception Room Subsciber Services	Birmingham, Ala	444
Eli Lilly & Company	Indianapolis, Ind	102, 103
EM-SCAN Inc	Springfield, Ill	402
Encyclopaedia Britannica Inc	Chicago, Ill	242
Endocrine Sciences	Calabasas Hills, Calif	212
Fiberoptic Medical Products Inc	Allentown, Pa	429
Genentech Inc	South San Francisco, Calif	313, 315
Genzyme Corporation	Cambridge, Mass	341
Gerber Products Company	Fremont, Mich	210
Gynex Inc	Vernon Hills, Ill	407
Healthdyne Technologies	Marietta, Ga	343
Hemocue Inc	Mission Viejo, Calif	340
Hologic Inc	Waltham, Mass	228, 230
I-Stat Corporation	Flemington, NJ	308
ICN Pharmaceuticals Inc	Costa Mesa, Calif	206, 208
Infrasonics Inc	San Diego, Calif	425
Intelligent Medical Systems	Carlsbad, Calif	448
International Technidyne Corp	Edison, NJ	435
J. B. Lippincott Company	Philadelphia, Pa	105
Kimberly Quality Care	Overland Park, Kan	431
Lederle Laboratories	Wayne, NJ	503

EXHIBITING COMPANY	CITY, STATE	BOOTH NUMBER
Marquette Electronics	Milwaukee, Wis	234
Mead Johnson Nutritionals	Evansville, Ind	406
MEDELA Inc	McHenry, Ill	446
Medex Infusion Systems	Duluth, Ga	309
Medical Data Electronics	Arleta, Calif	439
Medical Data Systems	Wayne, Pa	300
Medical Graphics Corporation	St Paul, Minn	333
Medical Research Center	New York, NY	545
Merck, Sharp & Dohme	West Point, Pa	434
Miles Inc Cutter Biological	West Haven, Conn	328, 330
Mosby–Year Book Inc	St Louis, Mo	101
N.I.C.H.D.	Bethesda, Md	339
Natus Medical Inc	Foster City, Calif	412
Neonatal Intensive Care	Santa Monica, Calif	349
Nuticia-Loma Linda Foods	Riverside, Calif	400
Ohmeda	Madison, Wis	325, 327
Oxford University Press	New York, NY	533
Plenum Publishing Corporation	New York, NY	450
Pourquoi Pas Inc	Mequon, Wis	535
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Annual Meeting of the Ambulatory Pediatric Association

JOINT TOPIC SESSIONS
Tuesday, May 5, 1:30 PM-5 PM

ADOLESCENT MEDICINE

Breast-Feeding Attitudes and Practices Among Adolescents

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Infants born to adolescent mothers are at increased risk for medical, psychosocial, and developmental morbidities against which breast-feeding (BrF) may mitigate. Yet, adolescents are less likely to BrF than older mothers. This study used a prenatal questionnaire to examine associations between pregnant adolescents' infant feeding attitudes and their feeding choice. The questionnaire included a list of potential BrF and bottle-feeding (BoF) benefits and barriers which subjects rated as either "important" or "not important" to their feeding decision. Initiation of BrF and problems encountered were documented during a post-partum telephone interview. 253 pregnant teens at four Denver inner-city clinics completed the prenatal questionnaire. The study population was 35.5% Caucasian, 35.6% Hispanic, 24.1% Black and ranged in age from 13-19 yrs (mean = 16.6 yrs). Prenatally, 63.9% of subjects planned to BrF. Ethnicity was associated with the infant feeding decision, with fewer Blacks choosing to BrF ($p<.02$). Those who selected BrF cited predominately "infant-focused" reasons (i.e. "healthier for baby"), whereas those who chose BoF gave more "self-focused" responses (i.e. "BoF is easier, more convenient"). Significantly more teens who planned to BrF rated 13 benefits of BrF as "important" at $p = <.02$, while significantly more of those who intended to BoF rated 6 of 11 barriers to BrF as "important" at $p = .01$. Following delivery, 65.6% ($n = 166$) of subjects completed a telephone interview (median 65 d PP). Of these, 62.0% initiated BrF, but only 23.0% continued beyond one month, and 74.4% reported one or more BrF problems. The most common problems were sore nipples (42.7%), leaking milk (30.5%), infant latch-on (22.0%), concern about milk supply (19.5%), and embarrassment about BrF in front of others (13.4%). This study suggests that, in order to increase BrF initiation and continuation rates among adolescent mothers, clinicians must not only promote the benefit of BrF, but also acknowledge and reduce the perceived barriers.

Predictors of Depression and Parenting Stress in Pregnant Teens

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Adjustment to the challenges of pregnancy and parenting varies among teens, yet the predictors of significant maladaptation have not been well studied. We hypothesized that: (1) pregnant teens who experienced more traumatic childhood conditions (such as parental loss, parental mental illness, or childhood abuse) would have a higher prevalence of depression; and (2) depressed pregnant teens would be more stressed by early parenting than non-depressed teens.

At the start of the 3rd trimester of pregnancy, 52 primiparous teens <18 years old (62% White, 25% Latina, 13% Black) completed the Beck Depression Inventory (BDI) and a questionnaire about 10 potential traumatic childhood conditions (TCC). Four months post-partum, 37 (71%) filled out the Parenting Stress Index (PSI) and the BDI. The prevalence of TCC was striking: 19% had lost a parent to death, 38% had been in non-parental care, 46% had alcoholic parents, and 23% had mentally-ill parents. Teens who reported ⩾5 TCC were more likely to be depressed (BDI ⩾16) than those with <5; (53% vs 15%, $\chi^2 = 6.36$, $p = .012$). Teens who were depressed prenatally were likely to continue to be depressed post-partum ($r = .7$). Teens with prenatal depression reported greater stress in parenting their 4-month olds than their non-depressed peers ($t = -3.3$, $p = .002$).

Screening pregnant teens for traumatic childhood conditions and prenatal depression identifies a sub-group at risk for on-going emotional problems and parenting stress. This group should be targeted for therapeutic interventions, both to reduce depression and to facilitate adaptation to parenthood.

The Meaning of Traumatic Injury and Death Among Adolescents in an American Indian Community

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Injury and mortality rates in the Native American adolescent population are among the highest of any ethnic group in the U.S. Most of these injuries are associated with complex behavioral and cultural risk factors. We undertook this study to develop a community explanatory model of the meaning of adolescent injury and fatality within a small western American Indian community.

Standard procedures in ethnography were employed: community entry, open ended in-depth interviews using key informant sampling, audiotape and field note transcription, review of field notes for key concepts, and community feedback. Initially, exploratory interviews were conducted with ten community leaders focusing on the historical, cultural and social context of the community. Interviews were then conducted with seven elders and 21 adolescents who were selected by key informants. Probe questions primarily focused on personal experience with death and serious injury among family and peers. Notes and transcriptions were coded for interview content.

Analysis of the interviews revealed that 90 percent of the adolescents had been exposed to traumatic deaths of close family members and friends. Although alcohol was implicated in most injuries and deaths, it was often preceded by the severance of a personal relationship. Bereavement was widely recognized by these youth to be a significant risk factor for a culturally defined syndrome of "spirit sickness", a potentially fatal illness. The revival of the indigenous ceremony to cure spirit sickness has become a source of divisive debate within the community. Because of the significance of the relationship between the living and dead in many Indian cultures, clinicians working with Native American youth should recognize the possibility of belief in "spirit sickness" and its potential to lead to a cyclic pattern of injuries and death.

Adolescents' Knowledge, Attitudes, and Behavior About Skin Cancer Prevention

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Excessive sun exposure during adolescence has been incriminated as an important modifiable risk factor for the rapid rise in skin cancer. The present study documents the opinions and habits of today's youth concerning strategies for sun safety.

150 female and 111 male university students rated the relationship of 20 items to skin cancer on a computerized questionnaire. Attitudes about suntanning and personal photoprotective behaviors were also assessed.

Perceived risk factors for skin cancer included blistering sunburns (96% of students), deep suntans (88%), tanning salons (87%), and total cumulative lifetime exposure (80%). However, 18% had at least one blistering sunburn during the past year, 47% worked on getting a tan each summer/vacation, and 11% used a tanning booth once or more during the past 12 months. 91% recognized the protective effect of sunscreens/sunblockers (SPF ⩾15), but only 42% regularly used these agents during warm weather. The students believed a suntan made them look healthier (79%), look more attractive (77%), feel more attractive (75%), and feel healthier (49%). Knowledge of skin cancer came primarily from the media (55%) and parents (29%). Suntanning practices were *most* influenced by the students themselves (79%).

The data demonstrate that many adolescents from this highly educated population are aware of the hazards of excessive sun exposure, but continue to practice poor sun safety habits. The short term personal benefits of suntanning appear to outweigh the long term consequences of this behavior. In addition to providing knowledge, preventive strategies must address issues of self esteem to help motivate adolescents and improve their utilization of sun protective resources.

BEHAVIORAL PEDIATRICS

Calming Effect of Intraoral Sucrose in Crying 6 Wk Olds

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Decreased crying and pain response following intraoral sucrose has been demonstrated in newborns. This is naloxone-reversible in rats and presumably opioid-mediated. To determine whether this distress reduction system was functional at 6 wks and modified by feeding, 15 normal infants were videotaped before and after two evening feeds after receiving 250 ul of 24% (w/w) sucrose soln or water by pipette to the midline anterior tongue in counter-balanced order. Solutions were delivered during an aroused state of ≥ 15 sec of sustained crying and the response observed until 2 min of continuous crying. *Per cent time crying* was affected by sucrose and prior feeding (Condition × Feed × Period ANOVA interaction F[2,26] = 3.4; P = .05). *Before* feeds, per cent time crying in the 1st min after sucrose was reduced relative to water (66±34 vs 82±17%; t = 2.3, P = 0.04), but not later. *After* feeds, there is no sucrose effect (all P>0.10). Mean latency to resume cry was longer following sucrose (12.9 vs 5.7 sec; t = 2.1, P = 0.03) only before the feed.

Conclusions. A rapid, brief calming effect of sucrose is present at 6 wks but abolished by prior feeds. The small amount of sucrose, rapidity of effect, and similar findings in human newborns and animals, implies that sucrose activates a central system regulating state, possibly mediated by endogenous opioids.

Screening Mothers for Depression

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The 8-item RAND corporation screening instrument for depression compares favorably with the lengthy Diagnostic Interview Schedule for Depression, but its scoring requires a logistic regression equation. We wished to assess the prevalence of depression among mothers of young children and to compare an easily scored 3-item version with the 8-item test. Subjects were eligible if they brought a child under 6 years old to one of 5 pediatric clinics (2 university, 2 private, and 1 military) during the summer of 1991. The depression questions were part of a 2 page anonymous questionnaire on family health. The 3-item version was scored as positive if the subject reported feeling depressed on at least 1-2 days during the past week AND had had two or more weeks in the past year or two or more years in their life when they'd felt sad or depressed. The questionnaire was completed by 667/752 (89%) subjects. The 8-item version was positive in 125/667 (19%). Those who were depressed were younger, had less education, and had lower monthly incomes than those who had negative screens (P<0.001 for all comparisons). Depression was more common in non-whites (29% vs. 16%, P<0.01), in the university and military practices than in private practices (24%, 20% and 12%, respectively, P<0.01), in single mothers (32% vs. 15%, P<0.001), and among smokers (30% vs. 16%, P<0.001). Compared with the 8-item version, the three-item test had a sensitivity of 82%, a specificity of 83% and a positive predictive value of 61%. Depression is common among mothers of young children. The easily scored 3-item questionnaire is simple, compares favorably with the RAND instrument, and could be easily incorporated into clinical pediatric practice.

Maternal Social Support and Childcare Problem-Solving Skills: Is There an Association?

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Background: Mothers deal with childcare problems everyday (eg, the 4 year old who runs into the street). This study examines the putative association between elements of mothers' social support and their skill in addressing 10 common childcare issues for children 1 month to 15 years old. METHOD: 128 mothers with easy access to telephones were recruited from 3 sites: 1) a university general pediatric clinic (n = 61), 2) a WIC clinic (n = 50) 3) a postpartum ward (n = 17). The participants completed a demographic data form, a verbal skills test (Chicago Tests of Primary Mental Ability), a social support scale (Maternal Social Support Index), and a depression scale (Center for Epidemiologic Studies Depression Scale). In a follow-up phone call within a week of completing the questionnaires, mothers were asked to respond to 10 problematic childcare situations (eg your 7 month old keeps waking up at night and you are exhausted-what would you do?). Their responses were scored using categories based on earlier work in adult problem-solving. Data analysis was performed using descriptive statistics, spearman correlations and stepwise multiple regression.

Results: 80% of mothers were white, 72% were married, 89% had at least a high school education, and 54% had annual income >$15,000. Total number of effective solutions (TNS) was significantly correlated with verbal scores (VS) (r = .38, p = 0.0001) and community involvement (CI) (r = .28, p = 0.01). Ability to assume the child's perspective (CP) was significantly associated with number of supportive adults available (SA) (r = .20, p = 0.02) but not with VS (r = .14, p = 0.13). Using stepwise regression with 6 demographic and psychosocial variables the best two variable model for TS included VS and CI ($R^2 = .21$, p = 0.0001). The best two variable model for CP was SA and VS ($R^2 = .09$, p = 0.01).

Conclusion: Elements of mothers' social support are more strongly associated with aspects of their childcare problem solving skills than annual income, number of children or depressive symptoms.

Do Foster Parents do it for the Money?

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Foster parents are often suspected of taking care of children for monetary gain. As part of a study of foster parenting, we interviewed 150 foster parents living in the Chicago area and asked questions about socioeconomic characteristics, motivations, and monetary expectations for foster parenting.

Only 17% of the foster families had outside incomes (not including foster parenting income) at or less than the poverty level as defined by the US Government. Outside incomes of greater than $20,000 per year were reported by 66% of the foster families, while 42% had incomes greater than $30,000. The mean reported yearly income from foster parenting was $9,065 with a range from $0-$47,000 and a standard deviation of $8,365. The mean amount received per child per month was found to be $324/per month (SD = 119), $11 per day or 45 cents per hour. 57% of the foster parents interviewed felt that the payment per month was too low. 40% reported suffering a financial loss when taking care of a foster child, and only 5% felt they were gaining financially. Closed and open-ended questions with regard to motivations for foster parenting revealed that almost all (95% or more) loved to take care of children and felt they were doing something useful. Income issues were at least somewhat important to 11% of the foster parents.

In conclusion, foster parents are not primarily dependent on fostering children for income. In fact, many feel foster parenting actually incurs a financial loss but do it because they like to take care of children.

Training in Behavioral Pediatrics Does Make A Difference!

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Despite the increased attention to training in the behavioral and psychosocial domains of pediatrics, no study has examined whether pediatricians with special interests and/or training in these domains perform differently than other pediatricians. To address this question, randomly selected pediatricians in the New Haven area participated in a study of 4- to 8-year-olds in their practices. Initially, each pediatrician indicated specialty areas of interest, residency rotations, and fellowship training. Children were then enrolled during 6-week periods in each office in 1987-88. At enrollment, the caretaker completed the Child Behavior Checklist (CBCL) about the child, and the pediatrician independently indicated on a specially designed form whether the child had any of 54 different behavioral or psychosocial problems. Each problem was later classified by 2 investigators into 3 categories based on the ease of clinical recognition: from "easy" (e.g., retardation due to Down Syndrome) to "difficult" (e.g., anxiety disorder).

Of the 50 pediatricians, 20% had fellowship training in behavioral pediatrics or related areas, 18% had a special interest and/or ≥2 residency rotations, and 62% had neither. Behavioral or psychosocial problems were detected in 28% of the 1,640 children enrolled. The rates of recognition increased with training: 24% (none), 31% (some), 46% (fellowship training) (P<.001). These differences persisted after stratifying for ease of recognition of the problem. Differences in the rates of recognition did not reflect differences in the children being seen, since the mean CBCL scores were the same in each of the three groups of pediatricians.

We conclude that training in behavioral pediatrics does substanially increase the ability of general pediatricians to recognize developmental or psychosocial problems.

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

The Epidemiology of Medically Attended Non-Fetal Injuries in Children and Youth From a Nationally Representative Sample

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The 1988 National Health Interview Survey - Child Health Supplement (NHIS-CHS) collected extensive information on the occurrence of injuries in a nationally representative sample of 17,100 children and adolescents ages 0-17. A household interview elicited information about all injuries during the preceding year that required medical attention. A total of 2,772 injuries were reported. Rates of reported injuries decreased by length of the recall period and varied significantly by age, nature, location and cause (E-code). Beyond age one, the rates remained relatively stable until adolescence when progressive increases reflected the onset of puberty for both sexes. Children age 1-5 experienced the vast majority of injuries at home from falls, burns, blows and cuts. Injuries at school (mostly falls) began to emerge at age 6-9, and at age 10-13 falls and sport injuries at school and other athletic settings exceeded injuries at home. At ages 14-17 an even greater increase in athletic injuries accompanied those associated with transportation. These data provide a framework to relate injury specific prevention research and a guide to target injury control interventions.

Age-Specific Prevalence Trends for Selected Hymenal Findings in Suspected Child Sexual Abuse Victims

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One thousand sixty-nine female suspected sexual abuse victims, ages 2-9 years, were examined with photocolposcopy. Age-specific prevalences for the following hymenal findings were calculated: crescentic configuration, annular configuration, rim narrowing, anterior concavity, posterior/lateral concavity, smooth and curved concavity, and angular and/or irregular concavity.

Analysis of age-specific prevalence trends using multivariant logistic regression supported the following conclusions: (1) there is a shift from apparent annular configuration predominance in pre-school girls (54.8% at age 2; 33.3% at age 9; $n=490$; $t=-3.301$; $p=0.001$) to crescentic configuration predominance in pre-adolescents (20.6% at age 2; 50% at age 9; $n=381$; $t=6.363$; $p<0.001$); (2) anterior concavities (7.1% at age 2; 1.7% at age 9; $n=49$; $t=-1.002$; $p=0.316$) and smooth, curved concavities (7.1% at age 2; 5% at age 9; $n=56$; $t=0.350$; $p=0.726$) follow prevalence patterns consistent with congenital, persistent features (stable trends); and (3) rim narrowing (8.4% at age 2; 41.7% at age 9; $n=223$; $t=8.822$; $p<0.001$), posterior/lateral concavities (2.6% at age 2; 16.7% at age 9; $n=75$; $t=3.624$; $p<0.001$), and angular and/or irregular concavities (4.5% at age 2; 13.3% at age 9; $n=79$; $t=1.976$; $p=0.048$) follow prevalence patterns consistent with acquired, persistent features.

Factors Associated With Tuberculosis Risk in Poor Urban Children

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There has been a dramatic increase in TB in NYC. In adults, homelessness, drug use, imprisonment, and AIDS are known risk factors. To determine which factors are associated with a positive PPD among poor urban children, we prospectively studied 725 children who presented to our clinic for routine health care from Sept.-Nov. 1991. For each patient we placed and read a 5 TU PPD, and determined: social risk factors (homelessness, parental arrest or drug use), Hx of TB or AIDS contact, country of origin of the child, BCG status, travel Hx of US-born children, household crowding, age, sex, and SES. Countries were categorized as low, moderate, or high risk according to WHO TB mortality rates. Travel Hx was coded as positive for visits to a moderate or high risk country ≥1 month. A positive PPD was defined as the average of two independent readings ≥10mm. The two readings on each patient were highly correlated (Pearson $r=.97$).

Fifty-two patients (7%) had a positive PPD, mean (SE) = 15.9 (0.6) mm. In a logistic regression model, social risk, moderate or high risk country, positive travel Hx, TB contact or BCG Hx were all significant independent predictors of a positive PPD (see Table). Household crowding, contact with AIDS and indicators of SES were not significant.

	Soc. Risk	Hi-Risk Country	Travel Hx	TB Contact	BCG Hx
Adj Odds Ratio	3.5	8.3	4.8	4.9	5.0
95% CI	1.4, 9.0	2.4, 29.4	1.5, 15.4	2.3, 10.3	1.9, 13.5

When classified as high risk based on the presence of any of the above risk factors, 50/52 patients with a positive PPD were correctly identified (sensitivity: 96%). These risk factors should be utilized in designing TB screening programs for poor, urban children. Furthermore, social factors associated with TB in adults must also be considered in the evaluation of children.

Fetal Outcomes of Pregnancies in Women With Delayed Childbearing

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First births to older U.S. women are occurring with increasing frequency. Most studies of the fetal effects of delayed childbearing have included too few older women for separate analysis of primiparae, or have failed to control for important confounding factors. Washington State birth certificates from 1984-88 were studied to see if the risks of low birth weight (LBW, <2500 gm), very low birth weight (VLBW, <1500 gm), or preterm delivery (PTD, <37 weeks gestation) were increased for older primiparous women compared to those aged 20-24 years. Logistic regression was used to adjust for socioeconomic status, smoking, prenatal care, prior fetal loss and maternal medical conditions. For 4019 white, singleton infants of mothers aged 35-39 years, adjusted odds ratios (and 95 percent confidence intervals) for LBW, VLBW, and PTD were 1.9 (1.5 to 2.3), 1.6 (1.0 to 2.7), and 1.7 (1.4 to 2.0), respectively. For 410 white infants of mothers aged 40 years or more, adjusted odds ratios for the same outcomes were, respectively, 2.5 (1.7 to 3.7), 2.3 (1.0 to 5.2), and 1.9 (1.4 to 2.7). Trend tests showed a direct relationship between each outcome and maternal age (in 5-year groupings) beginning with women aged 20-24 years ($p<.01$ for each test). Small numbers of births to older women precluded precise assessment of risk for other racial groups. This population-based study shows that, beginning at age 20 years, increasing maternal age is an independent risk factor for LBW, VLBW, and PTD in white, singleton, firstborn infants.

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

Management of Childhood Lead Poisoning: Clinical Impact and Cost-effectiveness

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No consensus exists regarding the preferred treatment of childhood lead (Pb) poisoning. We used decision analysis to compare four strategies: observation [OBS], EDTA provocation with no treatment if testing is negative [PROV], EDTA provocation with crossover to penicillamine (PCA) if testing is negative [EDTA/PCA], and PCA with crossover to EDTA provocation if toxicity occurs [PCA/EDTA]. Using literature data and hospital costs, we projected average life expectancy adjusted for long-term disability and medical treatment (QALE), and costs of treating a Pb poisoned child. We considered direct medical costs (MEDICAL) and total costs including the added cost of remedial education (TOTAL). Variables included: costs and quality adjustments of chelation, provocation, toxicity and learning disability; probabilities of toxicity, positive provocation testing and disability; and efficacy of chelation in reducing blood Pb level and risk of disability. Results were:

Strategy	QALE (yr)	Medical (per child)	Total (per child)
OBS	62.55	$463	$19,506
PROV	63.95	$786	$16,045
EDTA/PCA	66.12	$1,778	$11,117
PCA/EDTA	66.12	$2,032	$11,371

The results were most dependent on changes in costs of provocation and chelation, and probability of a positive provocation test. For example, when the costs of EDTA chelation and provocation exceed $1,500 and $580 respectively, PCA/EDTA becomes a more cost-effective strategy than EDTA/PCA. We conclude that chelation for Pb poisoning is a cost-effective treatment, particularly when the cost of remedial education is considered. For the estimated 200,000 U.S. children with blood Pb levels >1.2 μmol/L, more than $900 million may be saved and QALE improved with aggressive management.

Preventive Pediatric Health Care: A New Measurement Tool

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Measuring the amount of well-child care delivered in a clinic setting has been difficult to achieve. In this study a measurement tool was developed to retrospectively evaluate chart audit data in children (ages 0 to 5) from an urban, indigent population who receive health care in a community health program in Denver, Colorado. Immunization status, AAP recommended preventive pediatric health care visits, developmental, hearing, vision, and blood pressure screening, and anticipatory guidance in safety, nutrition, and family concerns were measured using a 95 percent confidence intervals (CI) scoring system (low-medium-high) in 386 patients who received a total of 7,595 patient visits. The evaluation revealed a large discrepancy for 0 to 5 year olds in immunization status (CI:86.0-92.9%-high) v. AAP recommended well-child care visits (CI:30.0-39.4%-low). These findings raise questions regarding the use of immunization status as an indicator of the amount of well-child care delivered and the practicality of the current AAP recommendations for routine health maintenance in a public pediatric clinic. The preventive pediatric care measurement tool developed in this study is a useful method to evaluate the amount of preventive care delivered in a pediatric clinic setting.

Prenatal Pediatric Visits: Implementation in a Pediatric Ambulatory Department by Pediatric Residents

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The prenatal pediatric visit (PPV) is important for establishing relationships and exchanging information between physician and parents. Because the American Academy of Pediatrics (AAP) recommends a PPV for all expectant parents, pediatricians should be familiar with recommended content and comfortable conducting PPV's. PPV's were implemented in our Pediatric Ambulatory Department-conducted by pediatric residents. Formal training was incorporated into the resident's ambulatory curriculum. This study examined a) resident and parental attitudes toward PPV's, b) the level of comfort each had participating in the visits and c) the PPV as a learning experience for residents.

Residents and parents were surveyed after each PPV conducted over a one year period. Residents were pre and post tested regarding their knowledge of recommended content. Ninety seven percent of mothers strongly agreed that the PPV was beneficial to them. All mothers felt comfortable interacting with the resident. All residents felt prepared to conduct the visits and comfortable interacting with the parent(s). All of the residents valued the PPV as a continuity experience and 85% felt that doing PPV's was good preparation for primary care practice. Resident knowledge increased as evidenced by improved post-test scores.

This study reaffirms the importance of the PPV in primary care practice. Attitudes of parents and residents were favorable, both enjoyed and benefitted from the experience. Residents felt more knowledgeable and comfortable with the PPV's as PPV experiences progressed.

Gender Differences in Pediatrician Communication During Primary Care

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Communication with adult patients differs by physician gender. We looked for differences in the pediatric setting. Audiotapes of 232 scheduled visits of pediatric patients with 52 resident physicians were coded by the Roter Interaction Analysis System which places verbal units into exclusive categories. Post-visit parent questionnaire results were analyzed. Visits with the 35 female physicians (FMDs) lasted longer (32 min) than those with the 17 males (MMDs) (27 min) (p = .014), though visit type and patient age did not differ. FMDs made a greater number of empathetic statements, asked more psychosocial questions, gave more information and engaged in more biomedical counselling. Unexpectedly, physician talk made up a higher proportion of total talk in visits with FMDs (.66 vs .62, p = .007). FMDs talked much more often to the child than did MMDs (p<.001). More maternal talk was classified as positive when mothers talked to FMDs (p = .01), and a trend toward more psychosocial talk to FMDs was noted (p = .058). Mothers visiting both FMDs and MMDs said they were very satisfied on global items which inquired about medical care and attention; however, mothers seeing FMDs were more likely to strongly agree (p = .024) with an item asking whether the doctor encouraged them to talk about their worries. Communication patterns of physicians have implications not only for training, but also for the outcome of care.

An Environmental Intervention to Reduce the Fat Content of School Lunches

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Current dietary recommendations call for children older than two years to reduce the consumption of fat to 30% of calories. We determined whether children in an elementary school lunch program would choose low-fat (LF) entrees meeting these objectives if such entrees were made available to them. Bellevue (Washington) School District provides its 6700 elementary students with a daily choice between two entrees. From September 1990 to June 1991 we recorded daily entree choices for 427,843 student meals (98% of meals). In March we began an intervention to increase the number of days when one of the two entrees was LF (30% of calories or less from fat). We calculated the nutritional content of each entree using a computerized nutrient database, recipe analysis, and information supplied by food manufacturers. The percent of calories from fat in the average meal selected each day was based on the proportion of students selecting each type of entree.

Before March, a LF entree was available on 29% of days and was selected by 41% of students. The average fat content for all the meals selected was 35.5% of calories from fat. By June, a LF option was available on 50% of days, and it was selected by 37% of the students. This intervention resulted in a reduction of the fat content of the average meal to 33.3% of total calories from fat.

We conclude that in this school district, guidelines for dietary fat were not being met. When given the option, however, many students selected a LF entree. Making more LF entrees available while still preserving choice may help reduce dietary fat consumption in school lunch.

GENERAL POSTER SESSIONS
Tuesday, May 5, 5 PM-9 PM

ADOLESCENT MEDICINE

Poster No. 1

Gender Differences Among Incarcerated Adolescents on STD Related Attitudes and Behaviors

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This study examined gender differences in STD related attitudes and behavior. A questionnaire was completed by 388 incarcerated adolescents. Attitudes, perceived barriers to care, intentions to change sexual behavior and self-reports of sexual behavior and drug usage were assessed. The median age was 16 and 79% of the participants were male. Both males 82% and females 64% were predominantly black. More males reported weekly sexual activity compared to females (males 41%/females 21%, p = .002). 57% of females reported fewer than two sexual partners in the past four months versus 11% for males, p = .0001. Males were more likely to use alcohol before sex (male 48%/female 29%, p = .009). Males used alcohol and marijuana more frequently (13+ times a year) than females (alcohol: males 47%/females 23%, p = .0004; marijuana: males 33%/females 12%, p = .001). Females intended to reduce their number of sexual partners more than males (females 75%/males 44%, p = .0001) and to abstain from using alcohol or drugs in situations that might lead to sex (female 69%/males 50%, p = .002). Females felt it was not OK to have sex with casual acquaintances (female 85%/males 50%, p = .0001). Different educational approaches may be needed for each gender when modifying risk for STD's.

Poster No. 2

Prevention of Chlamydial Infections in Infants Born to Teen Mothers

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Previous studies show that prenatal *Chlamydia Trachomatis* predisposes infants to conjunctivitis, pneumonia, and wheezing. To evaluate whether infants born to chlamydia positive teen mothers treated during pregnancy with erythromycin were at risk for these complications, we prospectively followed them for 1 year at Teen Pregnancy Service; infants of chlamydia negative teens were used as a control group. Maternal age, race, smoking, and infant birth weight and episodes of conjunctivitis, pneumonia and wheezing were collected. Infants were cultured for Chlamydia. Data were analyzed using T-test, Chi square and MANOVA. Ninety consecutive infants were enrolled, 28 born to chlamydia positive and 62 to chlamydia negative mothers. No difference in maternal age and race, smoking, or infant birth weight was noted between the two groups. All infant cultures were negative. MANOVA analysis showed no significant difference in pneumonia, wheezing and conjunctivitis between the two groups. Aggressive Chlamydia screening and treatment through special programs targeted to pregnant adolescents prevent complications in the offspring.

Poster No. 3

Effective Health Services for Adolescents: Developing a National Census of Comprehensive Services

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Providing health care to our nations' adolescents presents unique challenges. Delivering effective care to youth at risk for school failure, unintended pregnancy and substance abuse is particularly difficult. However, little is known about the distribution, organization or accessibility of different types of health care for teens. We developed a typology of adolescent health systems, services and outcomes. In 1990-91, we identified and surveyed sites providing comprehensive or integrated health services to adolescents in the US by soliciting program nominations from adolescent health experts, national organizations, state and local MCH directors, and foundation staff. Of the 660 programs nominated, 456 (69%) responded to the survey: 38% based in schools, 22% in hospitals, 21% in health or community centers, 8% in public health departments, and 11% in other sites. Most programs serving rural youth (n=54) are based in schools or health departments. Among all programs, 87% provide primary health care on site, 59% provide "comprehensive" health care, 46% provide access to services during evenings and 21% provide weekend access. Almost all provide health education and AIDS education, however, those targeting unsafe sexual activity were no more likely to provide contraceptives on site than those not targeting risky sexual behaviors (62% vs. 54%; p=.11). Only 30% of programs target dropout prevention and only 20% offer tutoring. Most programs (96%) have links with other community providers or agencies; these alliances are strongest in school-based programs. Despite a dearth of published data, 59% of programs have been evaluated. Describing system and service characteristics of adolescent health programs is important in helping to understand which program types are most successful at promoting health and preventing adverse outcomes for youth.

Poster No. 4

An Analysis of Adolescent Suicide Attempts: A Validation of the Expendable Child Measure

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The present study is an attempt to validate the Expendable Child Measure developed by Woznica and Shapiro (1990) as an instrument which differentiates between suicidal and nonsuicidal adolescents. Forty adolescents, ages 12-22, who were treated in psychotherapy at a Teenage Health Clinic were rated by their therapists on degree of suicidality and the Expendable Child Measure (ECM).

The ECM is a 12-item scale designed to assess the components of the expendable child syndrome, a cluster of feelings and perceptions reflecting a sense of being unwanted and/or a burden on the family.

Results of this study support previous findings (Woznica & Shapiro, 1990) indicating that suicidal adolescents were rated significantly higher on the ECM than were nonsuicidal adolescents ($p<.001$). These results provide further evidence of the validity of the ECM as a viable assessment measure in the area of adolescent suicide. The concept of expendability has important implications for the prevention and treatment of adolescent suicidality.

Poster No. 5

Serious Sports Injuries in a Pediatric Emergency Department

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Sports injuries (SI) account for 2.5 million emergency department (ED) visits and 100,000 hospitalizations annually in the U.S. To define the spectrum of serious SI (i.e., requiring hospitalization) in the pediatric ED, we reviewed our experience for 2 years, 1989 and 1990, at an urban children's hospital. Information on all patients with traumatic injuries requiring hospitalization was entered into a registry.

Registry data revealed 1112 admissions for injuries in 1989 and 1990, with 143 (13%) for SI. Thus, serious SI accounted for 0.6% of trauma visits and 0.14% of total ED visits. 83% of patients were male, with ages ranging up to 22 years. Serious SI included fractures (77%), abdominal organ injuries (7%), multiple trauma (5%), cerebral contusions or hemorrhage (4%), and dislocations (3%); ISS scores ranged from 1 to 25. The most frequently injured areas were the extremities (69%), head and neck (16%), and abdomen (8%). As compared with non-sports injuries, SI occurred in older patients (11.5 vs 7.3 years, $p<.001$) and more often in males (83% vs 64%, $p<.001$). ISS were slightly higher in SI (10 vs 8.8, $p=.021$). The type and location of injuries were also different between the groups. SI resulted in more fractures (77% vs 51%, $p<.001$) and neck injuries (4% vs 1%, $p=.002$).

We conclude that serious SI occur frequently in the ED, affecting predominantly male teenagers, and that the spectrum of injuries is dissimilar to those resulting from other mechanisms. The pediatric emergency physician must have knowledge of appropriate diagnostic tools and therapeutic modalities to treat serious SI and has the opportunity to gather epidemiologic data for the formulation of preventive strategies.

Poster No. 6

Unrecognized Pertussis in Adolescents

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Little information is available regarding the level of immunity to *Bordetella pertussis* among adolescents. In 156 healthy adolescents, we measured serum antibodies, by indirect ELISA technique, to the following pertussis antigens: filamentous hemagglutin, pertussis toxin, and 69K (outer membrane protein). In an attempt to identify intercurrent pertussis infection, we also measured a total of 43 repeat samples over the following five years. The estimated annual incidence of infection ranged from 6.1-12.2%. Only one of the adolescents with a significant rise in antibody titers reported a chronic cough during that interim time period. Among the 71 adolescents with intact immunization records, no significant relationship was found between the number of years since last immunization and level of antibody. These data suggest that adolescents represent a significant reservoir for continued transmission of pertussis. The findings also support the atypical nature of the clinical manifestations of pertussis in the older age groups and the concept that subsequent infection in previously immune persons may contribute to continuing protection against overt illness.

Poster No. 7

Patterns of Middle School Health Room Use

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Research on middle school health room (HR) use has been minimal. This study investigates the types and predictors of HR visits in two suburban middle schools. Data were collected on all 8868 HR visits, excluding those for routine medication, for the 89-90 academic year, and were systematically classified (interrater agreement, kappa 0.92).

Approximately 25% of visits were for injuries in schools A and B. Only 10.3% (A) and 12.2% (B) of this subset of visits required more than self-administered first aid. Specific somatic complaints precipitated 26.9% (A) and 20.4% (B) of total visits, and vague somatic complaints, 18.6% and 27.9%; of these, only 52.5% (A) and 57.5% (B) necessitated any nursing intervention. Visits not requiring nursing deliberation or not clearly health-related comprised 30.3% (A) and 23.8% (B) of total visits. Logistic regression was performed on the 6451 visits which involved nursing decision-making, looking for predictors of nonintervention. Those visits of students in low average academic ability groups were >2 times more likely to be for complaints not requiring nursing intervention ($p=0.0001$). Other support mechanisms for these students should be investigated.

Poster No. 8

Anticipatory Guidance for the Adolescent: Parental Concerns

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The opinions of parents regarding anticipatory guidance for teenagers have not been adequately investigated. This study was undertaken to document the priorities for routine adolescent health care from the parental perspective.

Ten private pediatric groups within the Central New York region participated in the study. 932 parents of 419 boys and 513 girls completed a computerized questionnaire which listed common psychosocial-medical issues of adolescence. The parents rated the importance of having these topics discussed with their teenager as part of *routine* health care. The percentage of parents who considered a topic important is recorded in the following table:

Topic	%	Topic	%	Topic	%
Nutrition	96	Abuse (physical, sexual)	87	"Safe Sex"	82
Alcohol/drugs	93	Abuse (emotional, verbal)	87	Family Illness	79
Sexual development	93	Depression	87	Family Relationships	76
Smoking	92	Body Image/ Self-Esteem	86	Safety	76
Exercise/Sports	92	Growth	86	Friends/peers	73
Self exam (breast, scrotum)	91	Menstruation	86	Wet dreams/ ejaculation	73
STD's	90	Contraception	84	Behavior/ discipline	72
Stress	89	Eating problems	83	School Issues	68
AIDS	89	Pregnancy	83	Masturbation	65
Skin Care	89	Suicide	83	Homosexuality	56

The results document that parents consider discussions regarding psychosocial-medical issues to be an important component of routine adolescent health care. Practitioners who wish to provide comprehensive services for young adult patients must be responsive to these parental concerns.

BEHAVIOR AND DEVELOPMENT

Poster No. 9

Intraoral Sucrose Affects Prepubertal Children's Responses to Experimental Pain

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To determine whether intraoral sucrose would exert an analgesic-like effect in prepubertal children, 27 children aged 8 to 11 years underwent the cold pressor test at 10°C on two occasions. Once, they kept 24% sucrose in their mouths, and once plain water. Treatment order was randomly assigned. Threshold was the time following arm immersion when pain was first experienced. Only data which satisfied predetermined criteria for validity when assessed blindly, were analyzed.

Results. Usable data were obtained from 12 subjects in the sucrose first and 7 in the water first groups. Threshold responses were affected by treatment condition [$F(1,17)=5.82$, $p=0.03$], regardless of day [$F(1,17)=0.3$, $p=0.6$] or order [$F(1,17)=0.11$, $p=0.7$] of testing, in a repeated measures analysis of variance. Intraoral sucrose prolonged threshold by 35% above the water baseline (17.7 vs. 13.1 seconds respectively).

Conclusions. The analgesic-like effect of intraoral sucrose, demonstrated previously in human infants and very young animals, appears also in older children. The cold pressor test at 10°C proved useful for studying pain responses, though some subjects had difficulties indicating threshold.

Poster No. 10

Bayley Infant Neurodevelopmental Screener (BINS) Prediction Profiles in Outcome of At-Risk Infants

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Prediction of later developmental function in at-risk infants is controversial. Presently, 3, 6, 9, 12, 18, and 24 month BINS versions are being standardized in conjunction with the BSID II. This study involves prediction of 36 month function, using the BINS 6, 12, 24, SES-COMP Index, and Postnatal Complications Scale (PCS).

A total of 421 subjects were evaluated at 6 months, 292 at 12, 184 at 24 and 120 at 36. The Bayley and BINS were given on the first 3 occasions, SES-COMP and PCS at enrollment, and the McCarthy at 36 months. On the BINS, conceptually grouped items (16-22) are scored optimal/nonoptimal and are summed.

If the BINS-6 and SES-COMP were optimal, 91% had normal 36-month cognitive function; if both were nonoptimal, 52% were later normal ($p=.003$). The same difference was true with motor function ($p=.002$). If the BINS-12 and SES-COMP were optimal, 96% were cognitively normal at 36 months; if both were nonoptimal, 8% were cognitively normal and 0% were normal motorically at 36 mo. ($p<.0001$). With an optimal BINS-6 or BINS-12 but nonoptimal SES-COMP, 86-93% were normal. An optimal BINS-24 and SES-COMP was associated with 94%-95% normal cognitive and motor outcome; however, SES-COMP added little. Multiple regression yielded Betas ranging from .54-.78 ($p<.0001$) for BINS variables and .11-.20 (ns) for SES-COMP and PCS in predicting 36-month outcome.

The BINS 6, 12, and 24 are predictive of later cognitive and motor function; addition of environmental or medical factors minimally enhances prediction. The BINS facilitates developmental surveillance and meets the 2-step AAP and PL 99-457 screening requirements.

Poster No. 11

Outcome of Survivors Weighing ≤1000 Grams Using the World Health Organization (WHO) Classification

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We used the WHO classification of impairments (I), disabilities (D) and handicaps (H) to compare 2 birth cohort groups (I:1979-1984 and II:1985-1989) of infants less than 1000 grams (ELBW) from 2 hospitals in a single county. Prospective assessments of neuromotor and visual function, hearing and mental development were performed and classified as normal or presence of I, D or H (not mutually exclusive). 417/861 ELBW born at the two regional hospitals during these periods were discharged alive (I:43%, II:52%). Subsequently 52 died and 78% (285/365) were followed for a minimum of 12 months (range 12-140 months). Demographic characteristics (birth weight, race, sex, maternal age, socioeconomic status) of both groups were similar except for gestational age, (I:mean = 28, II:mean = 27, $p<.05$). The overall assessment of the children at their last visit (mean 38 months) is given below:

Cohorts	Birth Weight	Normal	Impairments		Disabilities		Handicaps	
	Grams (n)		Minor	Major	Minor	Major	Minor	Major
I	≤800 (44)	16	18	10	10	3	6	1
	>800 (86)	45	28	13	11	5	7	5
II	≤800 (44)	19	16	9	4	6	5	3
	>800 (111)	51	39	21	12	11	9	6

Most of the ELBW infants survived without a serious H or D. There were no statistically significant differences in outcomes between the two groups, nor between children above or below 800 grams. Despite an increase in survival of ELBW children at BW less than 800 grams during time II, there appears to be no increase in I, D, or H.

Poster No. 12

DDAVP and Enuresis: What do we Know?

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Objectives: Desmopressin acetate (DDAVP) is promoted to treat nocturnal enuresis (NE) but indications are unclear. We reviewed all Randomized controlled trials (RCT's) to determine 1) short & long term efficacy 2) who responds? 3) dose-response curve and 4) comparison with other treatments. *Methods:* A Medline search from 1966 to May 1991, supplemented by contact with the drug companies, yielded 23 papers of which 18 were true RCT's (11 crossover & 7 parallel). Identifying marks were removed and each of us performed a blind independent review.

Results: The 18 RCT's included 354 subjects who had mostly failed some other type of treatment. All found decreased mean frequency of wetting ranging from 10 to 91%, but only 24.5% of subjects achieved short term dryness. One study of DDAVP responders only, directly tested longterm dryness and 21% stayed dry. In other studies which incidentally reported longterm effects, <<10% stayed dry after stopping DDAVP. There was wide variation in the type of patient included. Only 7 studies addressed prognostic factors. Children >9 years and with fewer initial wet nights do better. Four studies appear to include almost exclusively monosymptomatic NE children (ie primary NE, Positive family Hx & no urinary symptoms). Results were no better than those which included mixed symptoms. The dose-response issue has not been answered. Five studies which attempt to address it have methodological problems. Only one study compared DDAVP with conditioning alarms. Alarm patients had 10% fewer wet nights and a better long term result.

Conclusions: DDAVP reduces wet nights in children who have failed on other treatments, but it produces complete dryness in only a minority, and this is often a temporary effect. The literature focuses on short term efficacy. The true role of DDAVP will only be known when samples are carefully selected and prognostic factors accounted for, and more comparisons with other treatments are conducted, focusing on longterm outcomes. On the basis of current knowledge, DDAVP is inferior to conditioning alarms.

Poster No. 13

Does Treatment of Constipation at a Young Age Prevent Constipation and Stool Soiling in the School-Aged Child?

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The aims of the study were to describe the symptoms of constipation in infants, toddlers and preschool children and to evaluate if treatment in early life would prevent constipation and soiling in school-aged children. We report on 174 children ≤4 yr of age with idiopathic constipation who had entered school at follow-up. Parents reported <1 bowel movement (BM)/wk in 29% and <3 BM/wk in 58%, painful BMs in 67%, and stool withholding in 97%. An abdominal or huge rectal stool mass was present in 77%. Patients were treated with fiber and daily milk of magnesia and the laxative was slowly discontinued once normal BMs had been accomplished. A follow-up questionnaire mailed to the parents of these 87 boys and 87 girls was returned by 90. Patient characteristics were similar in those with and without follow-up. Follow-up age was 10±3 yr. Fifty-seven children (64%) had recovered, defined as no soiling with ≥3 BMs/wk and off medication and 33 (36%) had not recovered. Abdominal pain was present in 16%, stool withholding in 20%, constipation (<3 BM/wk) in 32%, the BMs clogged the toilet in 26%, laxatives were used by 17%, and soiling (1-7x/wk) was present in 18%. Treatment of constipation in young age prevented constipation and soiling in only 64% of school-aged children. Parents need to be counseled that infrequent stools, soiling or abdominal pain can recur or persist and are symptoms of constipation in the school-aged child.

Poster No. 14

Cranial Ultrasonography in Full-Term Cocaine-Exposed Infants

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Recent reports have described a significant increase in CNS abnormalities in offspring of cocaine using women.

The purpose of this study was to determine the frequency of such CNS abnormalities in infants born at or after 36 weeks gestation to known cocaine using women. We conducted a prospective study using cranial ultrasonography of 130 cocaine-exposed infants seen at Children's Hospital during a 22 month period. Newborns exposed to heroin, methadone, PCP and amphetamines were excluded. All ultrasound studies were reviewed by 2 pediatric radiologists. Infants from both the Intensive Care and normal newborn nurseries were included in the study. Most women also reported using alcohol and marijuana, in addition to smoking cigarettes during their pregnancy.

There were no structural abnormalities identified in any infant. 115 Ultrasounds (88%) were normal. 5 Studies (4%) revealed Grade I (germinal matrix) hemorrhage. 9 Infants (7%) had choroid plexus cysts, and one had a small non-specific echogenic focus adjacent to the frontal horn. Except for one infant born with arthrogryposis, all had normal neurological examinations.

No signficant intracranial pathology was identified in this study. Our conclusions are that prenatal cocaine exposure alone is not an indication for routine head ultrasound in full-term infants. In addition, we were unable to document an increased risk for serious CNS pathology in this population.

Poster No. 15

Evaluation of a Rapid Assay for Detection of Cocaine Metabolites in Urine Specimens

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Background. With cocaine use becoming an important consideration in many Emergency Department (ED) presentations, rapid diagnostic testing offers advantages to clinicians.

Methods. During a 10 month period, we evaluated the Abuscreen OnTrak Assay (AOTA) (cut-off value 300ng/mL, Roche Diagnostics) for detection of benzoylecgonine (BEC), the major urinary metabolite of cocaine. Results were compared to fluorescence immunoassay (FI) (cut-off value 80ng/mL), and confirmed by gas chromatography (GC/MS).

Results. 132 urine samples were analyzed. Reasons for obtaining tox screens included: mental status changes (31%), seizures (15%), penetrating trauma (15%), suspected exposure (14%), chest pain (10%). Compared to FI, sensitivity of AOTA was 68% (15/22), specificity 100% (110/110), PV(+) 100% (15/15), and PV(−) 94% (110/117). Since 7 positive specimens by GC/MS contained BEC at a value lower than the 300 ng/mL threshold of the AOTA, these results are not actually false negatives. Comparing detection methods using the 300 ng/mL threshold, AOTA had 100% sensitivity, specificity, (PV(+) and PV(−). The 22 positive samples originated from two subpopulations: 11 patients > 13 years old (x=15.9yr) and 11 patients < 7 years old (x=2.3yr). Median BEC levels were significantly greater in the older group (540 ng/mL versus 180 ng/mL, p<.01, Mann-Whitney U Test). Only 2/11 younger children had BEC levels that exceeded 300ng/mL.

Conclusions. The AOTA is a sensitive and specific screening test for cocaine use, especially in older pediatric patients. Rapidity of results (three minutes), small urine volume (0.5ml), and low cost ($2/test) are all advantages over conventional techniques. In young children, who may have passive exposure to cocaine and thus lower levels of BEC, the AOTA was less useful clinically.

Poster No. 16

Randomized Controlled Clinical Trial of Three Interventions in the Management of Persistent Crying of Infancy

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Objectives. Persistent crying in infancy occurs in 10% to 25% of infants less than three months of age. The objective of this study was to evaluate the management of this common problem.

Methods. Healthy infants less than three months of age meeting the criteria of persistent crying were randomly assigned to one of three groups for a two week period. All groups received an assessment, reassurance, and support by a health nurse. Group 1 received counselling regarding specific management techniques. Group 2 received a car-ride simulation device. Group 3 acted as a control. Mothers completed crying diaries, and pre- and post-intervention anxiety questionnaires.

Results. Thirty-eight mother-infant pairs were enrolled. There was a 25% reduction in daily hours of crying (p=0.02). There was no difference between groups. There was a 17% improvement in maternal anxiety (p<0.001), which was significant in the car-ride simulation group and the control group (p<0.001). However, the specific management techniques group had a baseline anxiety score which was within the normal range for women, and therefore a significant change could not be detected.

Conclusions. The natural history of persistent crying of infancy is improvement over time and specific interventions proved no better than reassurance and support alone in decreasing daily hours of crying. Maternal anxiety was within the normal range for women in all groups at the end of the trial, suggesting that support and reassurance are the most important strategies in caring for crying infants and their parents.

Poster No. 17

Left-Handedness as a Risk Factor for Accidental Trauma

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Left-handedness has been suggested as a risk factor for accidental trauma in adults. Accidents are a leading cause of morbidity and mortality in children. The purpose of this study was to examine left-handedness as a risk factor for accidental trauma in children and adolescents using a case-control method. A questionnaire focusing on handedness (method of Coren and Porac), past accidents, and parental perception was administered to 267 accidental trauma patients aged 6-18 years and 494 nontrauma controls in a pediatric emergency room. The frequency of left-handedness in the trauma group (16.5%) was significantly higher than the 10.5% in the control group (p<0.02 and odds ratio (OR) = 1.67). There was no difference found in female patients; however, in males, the trauma group frequency (20.1%) was higher than the control frequency of 11.2% (p<0.01, OR = 2.00). The proportion of left-handers who had previously been hospitalized for injury treatment (19.7%) was higher than the right-hander proportion of 12.0% (p<0.01, OR = 1.80). Parents of 25% of left-handers believed that their children had more accidents than average compared with 15.6% of right-handers' parents (p<0.02). Left-handedness appears to be a risk factor for accidental trauma in patients in a pediatric emergency department population.

Poster No. 18

Athyrotic, Lingual, and Goitrous Hypothyroid (HypoT) Infants Exhibit Distinct Differences in Screening and Definitive Thyroid Tests: Implications for Misdiagnosis

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113 infants with hypoT diagnosed in the Ky. Neonatal Thyroid Screening program since inception in Jan. 1980 were analyzed with respect to screening (Scr) and definitive (Def) thyroid tests, proximity of ScrT4 to ScrT4 cutoff levels and thyroid morphology on Tc scan (96 infants).

	Athyrotic (A)	Lingual (L)	Goitrous (G)	All Cases
# Cases	24	39	33	113
ScrT4 (ug/dl)	2.73*	6.0	4.26	4.4
ScrT4 < cutoff	4.64* (−2.7 SD)	2.2 (−2.7 SD)	3.44 (−0.87 SD)	3.24
DefT4 (ug/dl)	1.21*	6.23	3.21	3.78
ScrTSH (uU/ml)	327.6+	229.4	205.3	245.9
DefTSH (uU/ml)	572.0*	324.8	428.9	417.8
Free T4 (pg/ml)	9.16*	0.98	0.6	0.62

*diff from L (p<0.0001)
+diff from L and G (p<0.01)

ScrT4, DefT4 and Free T4 are lower and ScrTSH and DefTSH higher in A compared to L and G. Cutoff for suspect hypoT fell close to 1 SD from mean ScrT4 for L and G, suggesting that some L and G may be missed in T4 screens. ScrT4 and DefT4 in L may be misinterpreted as normal, which emphasizes the need for TSH determination in all suspect infants and the hazard in interpreting isolated T4 values in infants.

Poster No. 19

Hospitalization Of Children Born To Cocaine-Using Mothers

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The purpose of this study was to determine if children born to cocaine-using mothers have increased rates of hospitalization and whether they spend more medically unnecessary days in hospital. Forty-seven cocaine-exposed (C) infants were identified retrospectively. For each case, a non-exposed child was matched for race, mother's marital status and medical payment source. All hospital admissions prior to age 2 yrs (excluding admissions at birth) were reviewed using the Pediatric Appropriateness Evaluation Protocol.

C mothers were older (25.5 yrs. vs. 21.4 yrs., P<.0005) and had more children than the controls (P<.05). C infants were more frequently born prematurely (27.7% vs. 8.5%, P<.05). There were 21 hospital admissions in the C group and 11 in the controls. C children spent more days in hospital than the controls (106 vs. 31 days, mean 2.3 vs. 0.7, P<.05) but the proportions of medically unnecessary days were similar (17% vs. 19%.) For C children, 67% of hospital days were in those born prematurely. Infections, accidents and apnea were the major reasons for admission. These results demonstrate a hidden cost of maternal cocaine use and illustrate a way that interventions could have cost-saving effects.

Poster No. 20

Which Children Grow in Response to Foster Care?

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The study of growth after an intervention for maltreatment has received little attention, particularly in cohorts with pre and post intervention measurements. We investigated the growth patterns of 88 children who received care in the Pediatric Ambulatory Clinic (PAC) of St. Mary's Hospital, Waterbury, CT prior to placement in foster care and were then seen in the Foster Care Clinic at St. Mary's after being placed in foster care. These 88 children (followed 6/85 to 12/89) were 64% male, 69% Black or Hispanic, 58% were placed in foster care after age 2, they usually had only 1 foster home (66%) and most (78%) had been seen at PAC prior to age 12 mo. Fifteen percent had birthweights <2500 gr. and 18% had pre-foster care weight ≤10%. Using standard NCHS growth charts, the mean pre-foster care weight % was 45.7 compared to a mean post-foster care weight % of 55.9 (paired t=10.4; p<.001). Two independent ratings of children's pre- and post-foster care weight percentile patterns classified 44 children (50%) as improved after entering foster care, 21 (31%) as unchanged, and 17 (19%) with declining weight percentiles after placement. Children who were lighter (≤10%) prior to entry into foster care and those who were younger (≤12 mo.) when placed into care were more likely to have improved weight percentile patterns ($x^2=7.2$, $p=.02$; $x^2=7.1$, $p=.03$, respectively). Interestingly, prematurity, low birthweight, gender, length of and reason for placement did not predict which children grew after foster care.

We conclude that children who enter foster care, particularly those who are younger and lighter at placement, show significant improvements in weight after placement.

Poster No. 21

Developmental Evaluation of Young, Socially High-Risk Children: A Comparison of Three Screening Tests

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It is unresolved which developmental screening tests are appropriate for socially disadvantaged young children. We administered the Revised Gesell Developmental Examination (Gesell) and three screening tests (Gesell Revised Developmental Screening Inventory or RDSI, Denver II, and DDST) to 116 children, 15-30 mo., who were: without known developmental delay, ≥36 wks. gestation, Hollingshead SES V, on public assistance. 53% were Black, 47% Latino. Social risk factors included: single (77%) or adolescent (26%) parent, homeless (63%), Hx parental arrest/drug use (52%), maternal education <12 yr. (68%), Hx abuse/neglect of mother/child (16%). # of test items for the targeted age group (a measure of time for test) was: RDSI=76, Denver II=46, DDST=36.

Gesell results: 26 (23%) abnormal, 41 (35%) questionable, and 49 (42%) normal. After grouping results as abnormal/questionable or normal, sensitivity, specificity, and percent overreferral (# unnecessary referrals as % of total # children screened) compared to the Gesell were calculated for each screening test (see table). The RDSI and Denver II were statistically equivalent to the Gesell (McNemar's Test: p=.96, p=.76 respectively) and to each other (p=.58) in identifying children as abnormal/questionable. The DDST did not compare favorably to the Gesell (p<.0001).

	RDSI	DENVER II	DDST
Sensitivity (%)	88	82	16
Specificity (%)	88	65	100
Overreferral (%)	5	15	0

Either the RDSI or the Denver II, but not the DDST, are appropriate developmental screening tests for socially high risk young children. Choice of the RDSI or the Denver II may depend upon the time available for testing and the acceptable rate of overreferral.

Poster No. 22

Visual Reaction Time in Deaf and Hearing Children With Attention Deficit Disorders

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The neurobiologic basis of attention deficit disorders (ADD) remains poorly understood. Little is known of the effects of concurrent hearing loss on attentional patterns. Visual reaction time tests provide a precise measure of attention and response efficiency.

Fifty-two subjects (mean age 10.8 yrs., SD 2.9; 78% male) completed a computerized visual scanning and reaction time test. Subjects were grouped by diagnosis of ADD (positive findings on parent and teacher questionnaires and direct observation), and hearing status (hearing versus severe to profound prelingual hearing loss). There were 4 groups: Hearing ADD (n=14), Hearing controls (13), Deaf ADD (12), Deaf controls (13). Subjects responded to a target presented in either visual field with 3 cue conditions-no cue, valid, or invalid cues.

Split plot ANOVA revealed a significant effect of ADD on reaction time which was slower for both ADD groups (F=4.97 p=0.03). No effect of hearing status was found. There was also a significant effect of cue for all groups (F=3.72 p=0.03). Valid cues helped all groups; subjects with ADD were less attentive to invalid cues.

Early hearing loss and reliance on visual input does not appear to influence the altered patterns of visual reaction time demonstrated by children with attention deficit disorders.

Poster No. 23

Uncertainty and Mental Health in Mothers of Children With Chronic Illnesses

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This study tested the hypothesis that in mothers of children with chronic illnesses uncertainty surrounding illness outcome, efficacy of medical professionals, and personal resources to deal with the child's illness would be related to mental health. Based on qualitative interviews with mothers, a 15 item scale was created. The scale was administered to 109 mothers of 5-10 year old children who had a wide range of chronic illnesses. The scale had a high internal reliability ($alpha = .89$) and demonstrated convergent validity with items from two other measures. Maternal mental health was measured using the Ilfeld Psychiatric Symptom Index (PSI). Uncertainty was significantly correlated with the PSI total score ($r = .23$, $p < .05$) and with 2 of the 4 subscales (depression, $r = .23$, $p < .01$, and cognitive disturbance, $r = .35$, $p < .001$) but not anxiety ($r = .09$) or anger ($r = .15$) subscales. Illness uncertainty relates to mental health in these mothers. Interventions to reduce uncertainty may reduce mental health problems in mothers of children with chronic illnesses.

Poster No. 24

Correlates of Elevated Stress Among Parents of Infants With Disabilities

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Clinical experience indicates differences in family adaptation to disability in infancy. We tested whether child or family factors explain variation in parent stresses

97 married couples of infants ($M = 9.6$ mos.) with Down syndrome, motor impairment, or developmental dalay completed the Parenting Stress Index at entry to early intervention. Although the sample mean did not differ from the standardization norm, a subgroup (19.6%, $n = 19$) scored at a level indicating serious mental health concerns. This subgroup did not differ from other sample families in parent education, employment status, or income, nor in their child's age, gender, gestational age, health, or type or severity of disability. In this subgroup, mothers rated their support networks as less helpful ($F = 7.10$, $p = .006$), and both mothers and fathers perceived their family (on FACES-II) as less adaptable and less cohesive ($F = 3.82$, $p = .025$ and $F = 3.79$, $p = .026$) compared to the rest of the sample.

These data suggest that elevated parenting stress in families of disabled infants in related more to family dysfunction/isolation than to characteristics of the child.

Poster No. 25

Parent Protection Scale for Children Age 2-5 Years

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Although parental "overprotection" has been attributed to the vulnerable child syndrome, normative data about parental protection of children age 2-5 years are unavailable. We developed a 25-item Parent Protection Scale (PPS), utilizing 4-point Likert ratings of child-related parenting behaviors regarding autonomy, individuation, and separation.

Methods and Results: A community-based sample of 1002 parents was recruited, with successful completion of the PPS by 892 (92% white, 84% married, 88% middle-upper SES, and 90% mothers). The distribution of scores was normal, with a mean of 33.2 ($SD = 5.6$). Internal reliability was .73 and aggregate test-retest reliability (3-5 weeks later) was .86, $p = .001$. Principal components analysis and varimax rotation generated four factors (supervision, separation, independence, and control). One-way ANOVA for three age intervals between 22 and 62 months revealed significant differences between each group ($p < .05$), with a decline in protection scores for older children as expected.

Conclusion: The PPS provides a method of assessing parental protective behaviors toward children age 2-5 years.

Poster No. 26

Relation Between Parental Overprotection and the Vulnerable Child Syndrome

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Hypothesis: Despite their presumed interchangeability, we hypothesized that parental overprotection (POP) is independent of parental perception of child vulnerability (PPCV) to illness/injury.

Methods and Results: A community-based sample of 1002 parents was recruited, with successful completion by 892 (92% white, 84% married, 88% middle-upper SES, 90% mothers) of the Child Vulnerability Scale (Forsyth), a newly devised Parent Protection Scale for children age 2-5 years, and questions about clinical background and demographic data. High PPCV and POP were defined as 1 standard deviation above the mean. Correlates of high PPCV included a medical condition in the child ($\chi = 31$, $p < .0001$) and a history of life-threatening illness/injury in the child ($\chi = 15$, $p < .0001$). Correlates of high POP included younger child age ($t = 5.6$, $p < .0001$) and younger parental age ($t = 3.7$, $p < .0001$). Only 3% of the parents scored high for both PPCV and POP.

Conclusion: POP and PPCV are independent constructs, whose differentiation may have important etiologic, diagnostic, prognostic, and management implications.

Poster No. 27

School Functioning of Very Low Birth Weight Children

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Differences in school functioning are examined among 8- to 10-year-old children classified into 4 birth weight categories: extremely LBW (ELBW, ≤1000g), very LBW (VLBW, 1001-1500g), LBW (1501-2500g), and normal birth weight (NBW, >2500g). Almost 2,000 children ($N = 1868$) from 2 previous studies were re-contacted at early school age for parent and teacher interviews and developmental observations. Seven dimensions of school functioning are examined: parental reports of grade failure, placement in special classes, classification as handicapped, child's achievement test scores (Woodcock Johnson math and reading scores), teacher's rating of language and attention in the classroom (Adaptive Language Inventory), school behavior problems (Conners Teacher Rating Scale), and social competence (Harter Scale of Perceived Competence).

Comparisons across the birth weight groups reveal a higher prevalence of grade failure, placement in special classes, and classification as handicapped at lower birth weights, as well as lower test scores by ELBW children compared to all other groups. The lower math scores among ELBW compared to NBW children persist even when children with IQs < 85 are eliminated. ELBW children, compared to the other groups, had lower attention and social competence scores. ELBW and LBW children also were rated as having more school-associated behavior problems (total Conners and on hyperactivity and daydreaming subscales) than NBW children. There were no birth weight differences for anxiety and aggression subscales. Finally, regression results suggest that differences in birth weight are associated with grade failure and behavior problems, even controlling for demographic and neonatal health characteristics.

CLINICAL ISSUES

Poster No. 28

Coarctation of the Aorta: Failure of Early Detection in the Pediatric Patient

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Since premature cardiovascular disease is associated with late repair of coarctation of the aorta (COA), pre-school detection is optimal. We reviewed records of 50 consecutive patients > 1 year of age who had surgical repair of COA from 1979 to 1990 to determine the timing of referral and to evaluate the sensitivity of diagnostic clinical signs. Median age at referral was 8 years. Reasons for referral included cardiac murmur (24)(48%), hypertension (HTN) (8)(16%), decreased lower extremity (LE) pulses (1)(2%), combinations of the above (12)(24%), and others (5)(10%). A specific diagnosis of COA was rarely made. LE pulses were normal in 4(8%), decreased in 37(74%), and absent in only 9(18%). Although 47(94%) had upper extremity

(UE) HTN (>95%ile of age), only 25(50%) had systolic blood pressure (BP) >140 mm Hg. Thus, COA would have been missed in 82% if absent pulses were required as a diagnostic feature and in 50% if BP > 140 mm Hg was a necessary finding.

Comparison of data from this study and that of the previous decade reported from this institution (Pediatrics 69:159, 1982) suggests no improvement in early detection of COA by pediatricians. This study indicates that many children with COA have only mild HTN and have palpable LE pulses. Screening all children for COA by measuring UE and LE BP on at least one routine examination is mandatory.

Poster No. 29

Respiratory Signs and Symptoms as Markers for Pneumonia in Febrile Infants Less Than Two Months of Age

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Chest-x-rays are used routinely as part of a sepsis work up in infants in the Emergency Department to look for pneumonia as a source of fever, regardless of the presence of respiratory signs and/or symptoms. There has been questioning recently as to the necessity of obtaining x-rays if no signs or symptoms of respiratory illness are present.

A total of 169 infants less than two months of age presenting to a pediatric ED from April through October, 1991 had sepsis work ups performed when they presented with a temperature of 38°C or greater. Fourteen of these infants were excluded from the study because they did not have chest-x-rays done. Each infant was evaluated for respiratory signs and symptoms. Respiratory signs included rales, rhonchi, wheezing, retracting, grunting, flaring or focally decreased breath sounds. Symptoms included coughing, wheezing, dyspnea, tachypnea, nasal congestion or rhinorrhea. positive chest-x-rays were those with a focal infiltrate, whereas negative x-rays included normal readings, hyperinflation or bronchial thickening.

This study suggests that the presence or absence of respiratory signs and/or symptoms does not predict findings on chest-x-rays in febrile infants less than two months of age.

Poster No. 30

Predictors of Initial Glycemic Control in Newly Diagnosed Diabetic Children: A Randomized Trial

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Children and families experiencing the onset of diabetes face a multifaceted challenge. They must acquire knowledge and integrate the child's condition into their family life. Most central, initially, is the achievement of glycemic control. We studied 58 newly-diagnosed children participating in a randomized trial of home vs hospital care at the Montreal Children's Hospital. The home care group was managed with little or no recourse to hospitalization and was treated and taught diabetes care by a visiting nurse. Data were collected from enrollment forms, clinical records, Diabetes Knowledge Scale, Diabetes Regimen Adherence Questionnaire and a parent satisfaction measure. The ability of 8 variables to predict levels of HbA1c at 3 months post-diagnosis were assessed including the insulin dose on day 3 and at 1 month, child's age and sex, treatment group, knowledge, adherence and satisfaction with care. In univariate analysis only the insulin doses, age and sex predicted HbA1c. Treatment group did not, as subjects in both treatment groups, achieved equally good control (mean HbA1c 5.25 ± 1.42 hospital vs 5.52 ± 0.94 home; $P = .39$ Power>.85. HbA1c levels were lower in boys, older children and in those receiving more insulin/kg. Further, knowledge and adherence did not predict HbA1c, probably because mean knowledge and adherence scores were high and the phenomena of residual insulin secretion allows control within a range of family behaviours. The overall R^2 of the final model including age, sex and insulin dose at 1 month was .217 and $P = .004$. In this setting initial control is predicted primarily by fixed patient and treatment factors.

Poster No. 31

Reticulocyte Counts and Blood Smears in Jaundiced Infants

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Reticulocyte counts and red cell morphologic evaluations are often done to investigate the possibility of hemolysis in jaundiced newborns. However, these tests may be difficult to interpret because of analytic imprecision and limited reference range data. We used a large computerized database and data from a previous prospective study to determine the reference ranges and interhospital variability of reticulocyte counts (N = 801) and red cell morphology (N = 781) of term infants at two tertiary care medical centers.

The 95th percentile reticulocyte count for babies born at Stanford University Medical Center (Stanford) was 19%, compared with 7.5% and 5.7% at different times at the Medical Center at the University of California, San Francisco. Differences in reticulocyte counts were not due to a higher prevalence of hemolysis at Stanford: 2 to 3-fold interhospital differences in reticulocyte counts were observed in both Coombs-positive and Coombs-negative infants and in babies with and without early jaundice. Similarly, with the exception of polychromasia and tear drop cells, differences in red cell morphology due to apparent isoimmunization were small compared with differences attributable to hospital of birth.

Because manual reticulocyte counts and blood smear evaluations are poorly standardized, their routine use in jaundiced newborns should be abandoned. They are unlikely to be useful unless there is a strong clinical suspicion of hemolysis, the direct Coombs' test is negative, and the hospital laboratory can provide a reference range for newborns.

Poster No. 32

Are Well-Appearing Febrile Infants With Otitis Media at Risk for Serious Bacterial Illness?

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To determine whether febrile infants (FI) <2 months-old diagnosed with otitis media (OM) are at risk for serious bacterial illness (SBI), we prospectively studied 1,274 FI who presented to two pediatric emergency departments. A clinical impression of sepsis, a physical examination (PE), and a standard evaluation for sepsis were performed on all FI. 60 FI with OM were identified from a group of 827 well-appearing FI with no evidence of bacterial infection other than OM on initial PE. Of those well-appearing FI with OM, 1.7% (1 of 60) had a SBI (one urinary tract infection) as compared to 10% (80 of 767) of FI without a bacterial source ($p < 0.05$). The relative risk of SBI in FI with no bacterial source on initial PE compared to those with OM was 6.26 (95%CI: 0.89-44.2). No FI with OM had bacteremia or bacterial meningitis. In the population studied, well-appearing FI with OM were at a low risk for SBI. These data suggest that it may be possible to modify the standard evaluation for sepsis in well-appearing FI <2 months-old with OM.

Poster No. 33

When To Assess the Health of Children Entering Foster Care

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Children placed in foster care are at high risk for unrecognized and untreated health problems. The legally mandated model in Maryland is for all children to receive a brief health screen within 5 days of entry into care and a comprehensive assessment by 60 days for those still in care. Because of implications for case planning and resource allocation, this study was designed to determine if it is possible to predict, using data at the early screen, which children will be available for the later more comprehensive exam. The sample consisted of 1246 children who entered foster care in Baltimore between Sept. '89 and Feb. '91. Using logistic regression, we tested an a priori model consisting of 22 theoretically meaningful variables arranged in 4 blocks: demographics; placement circumstances; family situation and problems; and the child's health. Overall the model did not reliably predict whether a child would appear for the comprehensive assessment. Therefore, initial services to these children need to be planned without regard to length of time in care. All children, upon entry into foster care, need a comprehensive assessment and rapid follow up on recommendations.

Poster No. 34

Follow-up After Placing Tuberculin Skin Test: Which Method is Best?

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We prospectively compared four different methods of following up tuberculin skin tests in an urban pediatric clinic. Of the 274 patients tested over 10 months, 80% had PPDs placed for routine screening, 13% were tested because of foreign birth, and 7% were placed for purposes of diagnosis or contact evaluation. Ten (4%) of the tests were positive; there were no positives among those who were tested for screening purposes only. Follow-up was best for patients who had a scheduled appointment to have the skin test read (34% were seen and 82% had some form of follow-up), intermediate for those called by a clinic nurse to ask about reactions (16% were seen and 80% had some form of follow-up), somewhat poorer for postcard follow-up (9% were seen and 52% returned postcards), and worst for those families who were told to call or return to clinic if they noted any type of reaction (7% were seen and 9% of parents called), P<.001 for differences between groups.

Even in clinics with a poor show rate for scheduled visits, we recommend that high risk patients receive appointments for follow-up of tuberculin skin tests. The practice of relying on parents to read and report results should be abandoned.

Poster No. 35

Failure of Standardized Respiratory Rate Measurement to Detect Pneumonia in Febrile Infants

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Although tachypnea is considered an important predictor of pneumonia, there are no definitive standards for normal respiratory rates (RR) in febrile children less than 2 years old. We attempted to validate a standardized method for determining RR in febrile infants seen in an acute care setting. Eligible patients were 0-24 months old with a temperature >38.0° in whom a chest radiograph (CXR) was ordered. Children with acute stridor or wheezing were excluded. Examining physicians obtained RR by placing a stethoscope on a study patient's chest and counting respirations for 15 seconds on 3 separate occasions. The results were averaged and multiplied by 4. The physician recorded the state of the child during each measurement (sleeping, quiet, feeding, crying) as well as the patient's temperature. CXR were classified as no pneumonia, pneumonia or indeterminate by 2 radiologists. Receiver operator characteristic curves were constructed to ascertain the best cut-off value for tachypnea. Of the 91 children enrolled radiographic evidence of pneumonia was present in 22 (24%), with no pneumonia in 66 (73%); 3 CXR were classified as indeterminate. The sensitivity and specificity of RR in predicting pneumonia was maximal at 58 (sensitivity=41%, specificity=79%, PPV=39%, NPV=80%). However, using this definition, tachypnea was of only borderline significance in predicting a positive CXR (P=.053). Mean RR of patients with no pneumonia was similar to those with a positive CXR (50 vs. 54, P=.38). Height of fever did not correlate with RR in patients with no pneumonia (r=.01, P=.9) RR was similar regardless of the state of the child (P=.54). We conclude that this method for obtaining RR is of limited utility in the acute care setting.

Poster No. 36

Consumer Use of Tympanic Thermometry: Is It Reliable?

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A tympanic thermometer designed for consumer use was placed on the market in October 1991. The reliability of temperature readings taken by tympanic thermometry has been shown to be dependent on temperature taking technique. This study was designed to determine if nonmedically trained consumers could obtain reliable temperature readings with this new instrument. Parents of 76 children presenting for outpatient or inpatient care were enrolled. They were given a Thermoscan HM-1 tympanic thermometer with its instructional manual and were instructed to familiarize themselves with the instrument and its use. The proper use of the thermometer was also demonstrated by one of the investigators to half of the parents. When parents considered themselves comfortable, they were asked to take a tympanic temperature on their child as well as a temperature by whatever method they usually used at home. Temperature readings were then obtained using the same methods by a physician investigator. The absolute value of the difference between tympanic temperature as measured by parents and physicians was calculated (0.40 F). This was then compared to the absolute value of the difference between temperatures measured by parents and physicians using conventional thermometry (0.48 F). This difference was not statistically significant (p=.28). Demonstration of proper technique did not influence agreement between parent and physician tympanic temperature readings (p=.30). The temperature readings reported by parents using tympanic thermometry should be considered as reliable as those taken by more conventional techniques.

Poster No. 37

Upper Urinary Tract Deterioration With Myelomenincocele

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Almost all infants and children with myelomeningocele (MM) have a neurogenic bladder. Though upper urinary tract deterioration (UUTD) is well recognized as a complication of the neurogenic bladder, there is a paucity of data on its incidence by age and outcome. We reviewed the development of UUTD and management among a MM population.

There were 425 newborns; length of follow-up ranged from 6 months to 30 years. UUTD as defined by hydronephrosis on imaging studies was noted in 85 children. Of these 85, 75% had hydronephrosis present prior to 3 years. The incidence of UUTD was 6% at birth, 8% between birth and 1 year, 3% between 1 and 3 years, 2% between 3 and 5 years, and 4% between 5 and 15 years. The hydronephrosis resolved or improved in all 53 of those treated with a vesicostomy, whereas 11 (42%) of 26 managed with bladder catheterization (CIC) demonstrated worsening (p <.001).

We speculate that urodynamic evaluations during the first 3 years and increased parental compliance with CIC and medications may decrease the incidence of UUTD within the MM population.

Poster No. 38

Tracheostomy Speaking Valves In The Pediatric Population: Experiences and Recommendations

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Improved survival of children with respiratory distress requiring ventilator support has resulted in an increased number of children with tracheostomies. These are performed to facilitate prolonged ventilation but prevent phonation. Lack of vocal output causes delay in speech and language development and is a major concern for parents, developmentalists and language pathologists. Trachestomy valves are handy one way valve devices which allow air to enter lungs during inhalation but deflects air during exhalation to pass through the larynx creating sound by vibration of vocal cords.

We report our experiences with 37 children with tracheostomies who were provided speaking valves in a pediatric speciality hospital. Twelve of the patients were still ventilator dependent when the valve was applied whereas others had open tracheostomies. Subjective and objective observations were obtained by physicians, speech pathologists and nurses. No medical complications were encountered during application.

Our findings during this non-controlled study showed that for children under 24 months, use of Passy Muir valve facilitated earlier emergence of vocalization and vocal play, increased variability of sound and earlier emergence of consonant sound with babbling. For patients aged above 24 months, additional changes included increased length, and volume of utterances, improved vocal quality and improved use of syntex and semantics. Improved communication skills facilitated an overall improvement in other developmental functions. Language is a continually active process during early infancy and provision of expressive language for tracheostomized patients by the use of speaking valves facilitates communication and promotes socialization and developmental gains.

Poster No. 39

Immunization Status of Children With Spina Bifida

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Children with chronic illness, especially neurologic diseases, may be at increased risk of underimmunization. We reviewed immunization records of 120 children seen in a large multidisciplinary myelodysplasia clinic and examined the influence of socio-demographic, clinical, and primary care provider characteristics on immunization completeness.

Only 58% of children 2 yrs or older and 55% of children 7 yrs or older had completed the immunization series recommended by the American Academy of Pediatrics. Lower immunization levels at 24 mos occurred in older children, those insured by Medicaid, and those whose mothers completed 12 school yrs or less. At 7 years, no clinical or demographic variables were significantly associated with immunization completeness. Seizure history did not predict decreased use of pertussis vaccine. 99% identified primary care sources. Immunization delay, defined as administration more than 60 days after the recommended age, increased through the 18 mo vaccines to 50% and declined to 24% at school entry. Sizable numbers of children with spina bifida are underimmunized despite having an identified source of primary care.

Poster No. 40
Aerosolized Epinephrine (AE) Use in the Treatment of Croup

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We prospectively studied children with croup, to determine whether a subpopulation of the patients receiving AE could be observed in the Emergency Department (ED) and then discharged home. 49 patients, aged 3 months to 6 years, made 52 visits to the ED for croup. 38 met the study criteria and did not have a history of previous airway manipulation. These patients were assigned croup scores (CS), received mist therapy, and were again scored after 30 minutes. At that time the need for AE was determined. All patients who received AE were admitted to the hospital and followed with serial CS. After 2 hours, 7 patients had CS <3, no supplemental oxygen requirement and had received only one AE in the ED. None of these patients received subsequent AE. 13 patients received AE with a mean initial CS of 4.82 (range 0-17). Only two patients required subsequent AE after admission. The initial CS was not predictive of the need for further AE. We conclude that children receiving AE treatment for croup can be discharged home after a 2 hour period of observation if they clinically appear well to an experienced physician, and have received only one AE treatment during the observation period.

Poster No. 41
Efficacy of a Herbal Tea Preparation in Infantile Colic

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The present study evaluated the effect of a herbal tea (HT) preparation (Calma Bebi, Bonomelli, Italy) in infantile colic. This prospective double-blind study investigated healthy infants, aged 0-2 months, 33 on HT and 35 on placebo. There were no significant differences between groups regarding male/female ratio, feeding habits, social class, birth weight and perinatal history. Evaluation included scoring of pain improvement or elimination of colic and number of night wakings. HT eliminated the colic in 19/33 (57%), whereas placebo in only 9/35 (26%) ($p<0.05$). The mean pain improvement score was significantly better in HT-treated infants compared to placebo (1.7;pm0.3 versus 0.7;pm0.5, $p<0.01$). No significant differences were noted between groups regarding number of night wakings.

We conclude that the above herbal tea preparation is probably better than placebo in improving infantile colic. These preliminary results should be confirmed in future large-scale studies.

Poster No. 42
Otitis Media: A Vulnerability Factor?

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Factors that contribute to developmental vulnerability were examined in a four-year follow-up of first-grade children who as infants had participated in an investigation of the relationship between recurrent otitis media and developmental status. The children in this low income, inner-city sample attained Bayley scores within normal at 14 months of age (MDI = 102), but they experienced significant decline in their language and developmental status regardless of their history with otitis media (Mean McCarthy GCI = 89, Mean Peabody Picture Vocabulary Test = 79). Children were raised by women who were poorly educated (61% < high school), single (81% unmarried), and on medical assistance (91%). Using hierarchial multiple regression analysis, exposure to otitis media during infancy or toddlerhood did not contribute to language or development, but early maternal behavior facilitated children's language development ($p<.02$) by serving as a compensatory factor, counteracting any potential impact of recurrent otitis media. Results support a threshold model of risk, suggesting that otitis media does not necessarily pose an additional stress to the language and cognitive development of low income, inner-city children.

Poster No. 43
Single-Dose Ceftriaxone for the Treatment of Acute Otitis Media With Effusion

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Children aged 18 months to six years with acute otitis media with effusion (AOME) are eligible for enrollment in a randomized, single-blinded trial comparing a single dose of intramuscular ceftriaxone (50 mg/kg, max 1 gm) with a ten-day oral regimen of cefaclor (40 mg/kg/d div BID). Patients are followed by phone at 43-72 hours, and return visits to a validated otoscopist at 7-10 days, 3 weeks, and every 3-4 weeks thereafter until resolution of effusion or referral to otolaryngology at 90 days.

To date, 24 patients received ceftriaxone (R) and 19 patients received cefaclor (C). Two R patients were lost to follow-up. All parents reported symptomatic improvement within 72 hours. There was no difference between groups in time to resolution of pain or fever. All patients had persistent effusion at 7-10 days. One patient in the R group and two patients in the C group had recurrent AOME (recurrent pain and inflammation) within two weeks.

Complete follow-up data are available for 15 R and 15 C patients. Four patients in the R group and three in the C group had recurrent AOME within 90 days. Four patients in each group had persistent effusion requiring referral. Pressure equalization tubes were placed in one patient from each group for persistent effusion unresponsive to further courses of antibiotics prescribed by otolaryngology. There were no differences between groups in rate of resolution of effusion, number with persistent effusion, or number requiring surgery, although current sample size limits the power to detect a difference.

We anticipate enrollment of 100 patients by April 1992.

Poster No. 44
Asthma Claims From Children Receiving Medicaid/AFDC as a Basis for Selective HMO Enrollment

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Objective: To curb healthcare costs, the State of Maryland has contracted with HMO's to allow Medicaid/AFDC recipients to enroll in an HMO while Maryland pays the capitation rate. This study examined whether asthmatic children were as likely to enroll in HMO's as other children. *Methods*: All children (under 21 years old) from Baltimore who were continuously enrolled in Medicaid/AFDC during fiscal year 1987 and who had no HMO experience during or prior to that time were selected for the study. Non-blacks were excluded from analysis due to insufficient sample size. The study group contained all children from this population who submitted a claim for asthma during fiscal year 1987. The remaining children who did not submit an asthma claim formed the control group. The groups were compared based on the rate of enrollment into an HMO for the first 6 months of fiscal year 1988.

Results: A total of 40,861 children qualified for the study, and 446 (1.1%) of them submitted at least one claim for asthma during fiscal year 1987. Among the children who submitted a claim for asthma, 4.0% (18/446) joined an HMO, while among children who did not submit an asthma claim, 5.7% (2,314/40,415) joined an HMO (p = NS). When children under six were examined separately, 4.4% (12/269) of those with asthma claims joined HMO's while 7.9% (1,144/14,457) of those without asthma claims joined an HMO ($p < 0.05$). In children over five, the enrollment rates were 3.4% and 4.5% respectively, but the difference was not significant statistically.

Conclusion: Pre-school children who had submitted an asthma claim in the previous year were 44% less likely to enroll in an HMO than pre-school children who had not submitted a claim for asthma. Since capitation rates are not adjusted for the presence or absence of chronic disease, such biased HMO selection could interfere with cost containment goals.

Poster No. 45
Tube Feedings Help

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Children with neurologic disabilities (ND) often are poorly nourished despite prolonged oral feedings. We studied effects of tube feeding such children. We reviewed growth data on all CMH Nutrition Clinic pts with: ND, % ideal body weight for height age (IBWH) $<90\%$ on oral feedings, and consequent tube feedings (TF). Parents were surveyed via mailed questionnaire (PQ) on changes they perceived in their children, comparing before vs. after TF (1 = much worse, 5 = much better).

29 pts (17 M, 12 F, mean age at 1st visit 38 mo.) were followed on TF for a mean of 22 mos. Tubes were nasogastric (NG; $n = 15$), gastrostomy after NG (GT; due to intolerance or reflux surgery; $N = 10$), and GT ($n = 4$). Mean %IBWH improved from 74% to 94% ($p<.0005$): NG (73% to 89%, $p = .002$) and GT (75% to 99%, $p<.0005$). 3 pts (2 GT, 1 NG) died, none of TF complications. 17 PQ were returned (10 NG, 7 GT). Mean score for child's health on TF vs. pre-TF was 4.7 and for child's mood, 4.6. No change was reported in care time.

We conclude: (1) both NG and GT feedings safely improved nutrition in these children and (2) this objective improvement was often accompanied by other, subjective, improvement. These data suggest that TF, NG (non-operative) when tolerated, warrants wider use and further evaluation.

Poster No. 46
Hepatitis B Screening of Indigent Mothers: Practical Aspects

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Universal screening of pregnant women for Hepatitis B is recommended by the Centers for Disease Control in order to prevent perinatal transmission of disease which may have severe sequelae. Whether this is cost-effective has been controversial. The purpose of this study was to evaluate the practical aspects of screening which affect cost-effectiveness in a large, inner city hospital.

All women admitted to labor and delivery between July 1, 1990 and June 30, 1991 were tested for hepatitis B surface antigen (HBsAg). Infants were treated with immune globulin if the results were positive or unknown at 12 hours of age, and with vaccine if results were positive. Follow up was through community health clinics.

Twenty-seven of 7,431 infants were born to HBsAg positive mothers, for a carrier rate of 0.35%. Twenty-six of the 27 infants received immune globulin by 12 hours of age. In addition, 2,631 doses of immune globulin were administered to infants of non-carrier mothers because HBsAg results were not available by 12 hours of age. In follow up, nine of 27 infants received the second dose of vaccine at age one month, and two of 16 eligible for a third dose at six months received it. Six of 27 infants are up to date for the vaccine series.

Evaluation of the screening program in one public hospital has revealed that the carrier rate in this indigent population is no higher than in the population at large. Infants of carrier mothers were successfully identified, but follow up was extremely poor, which may limit the clinical effectiveness of the program. Cost was increased by provision of unnecessary and expensive immune globulin. Published cost-effectiveness analyses which do not take these problems into account may not apply to indigent populations.

Poster No. 47
Infrequency of Adenotonsillar Hypertrophy (ATH) as a Proven Cause of Obstructive Sleep Apnea (OSA) in a Tertiary Care Children's Hospital

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Background: ATH is being increasingly cited as a primary cause of both OSA and related day and nightime clinical problems (snoring, enuresis, learning and behavior problems). This has led to an increasing number of adenotonsillectomies (T and/or A) performed due to presumed OSA. ATH as a major cause of OSA, and OSA as a major cause of the problems cited, have not been confirmed by methodologically rigorous studies.

Research question: In our tertiary care children's hospital in which about 2000 T and/or A are done/year, how many children studied in our sleep laboratory have OSA due to ATH?

Methods: Records of 630 children studied by formal polysomnography since 1981 were reviewed. OSA was defined as an apnea/hypopnea index of more than 10/hr. Where no obvious craniofacial abnormality (eg Pierre-Robin) or C.N.S. cause was found, medical records were reviewed for clinical or radiologic evidence of ATH.

Results: Of 69 children with OSA, the majority (45) had facial syndromes or other obvious causes of OSA. Of the remainder, careful chart review identified additional cases of facial syndromes or CNS abnormality and only 8 cases of OSA due to ATH alone, or fewer than 1 per year.

Conclusion: In our hospital proven OSA is rarely caused by ATH. There may be a referral bias; however ours is the only pediatric sleep lab in the area. ENT surgeons use clinical criteria to diagnose OSA, but the measurement properties of these criteria are not well established. More research is required to assess the validity of clinical assessment, the clinical importance of ATH and OSA, and whether surgery is effective.

Poster No. 48
The Reliability of Mid-Stream Urine Culture From Circumcised Male Infants Compared to Supra-Pubic Aspiration (SPA)

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Included in this prospective study were 31 male circumcised infants, aged 10-60 days who needed urine cultures. In each patient, a mid-stream urine specimen was collected after cleansing the penis with antiseptic solution while the baby was on his back. When the bladder was full again, a SPA was also performed. The results of the urine cultures for each patient were identical in the specimens obtained by SPA and mid-stream. In 22 infants the cultures were sterile and in 9 they were positive with the same microorganism being cultured in both instances.

The median time required to obtain mid-stream urine was 7.4 minutes (range 1-115 minutes). The number of attempts at SPA required in order to obtain urine ranged from 1-4, mean 1.6. This preliminary result suggests that in circumcised male infants, the mid-stream method of obtaining urine for culture is as reliable as supra-pubic aspiration.

Poster No. 49
Yield From Stool Testing of Pediatric Inpatients

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Although stool testing is done noninvasively, it may be ordered indiscriminately for hospitalized patients, generating unnecessary expense. Adults with nosocomial diarrhea almost always have negative stool cultures (SC) and ova and parasite exams (OPE). We hypothesized that too many stool tests are ordered for pediatric inpatients and that we could identify criteria to be more deliberate without sacrificing diagnostic ability.

We reviewed records of all SC, OPE and Clostridia difficile toxin assays (CDA) done on pediatric inpatients, ages 3 days to 18 years, at Thomas Jefferson University Hospital for a 1 year period. Charts were reviewed for positive cases, each with 2 controls matched for age and test.

Of 250 admissions with SC, seven admissions (2.8%) had positive cultures. Of 63 admissions with OPE, one was positive (1.6%). Of 40 admissions with CDA, seven admissions tested positive (17.5%). Only 18/598 (3%) of all tests were positive. Costs of negative tests to patients totaled $26,084 (estimated costs nationally total $14.8 million).

More patients with positive SC than control patients had fever $\geq$38°C [71% vs 21% (chi-square: $p<.05$)]; but relying on this sign missed 29% of children with bacterial infection. A blood leukocyte (WBC) band count of $\geq$10% was 100% sensitive and 79% specific in identifying patients with positive SC. There was no relationship between SC results and age, total WBC or WBC segmented neutrophil count and no relationship between CDA results and all of the above characteristics. C. difficile was the most common pathogen found (6/9) in patients developing GI symptoms after admission; however Salmonella and Shigella were also significant causes (3/9).

In summary, there is low yield from stool testing of pediatric inpatients, especially from OPE. CDA has highest yield and is most valuable for children with nosocomial symptoms. Unlike findings in adult patients, bacterial pathogens can cause nosocomial GI symptoms in children. Although few criteria were found to reduce stool testing, pediatricians might consider limiting stool cultures to children with band counts $\geq$10%.

EMERGENCY MEDICINE AND CHILD ABUSE

Poster No. 50
Preschool Aged Victims of Child Sexual Abuse

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Preschool aged children represent a significant proportion of hidden and disclosed child sexual abuse. The purpose of this study is to describe abuse reported by this youngest group of victims.

Of 1327 children under age 15 years evaluated at a sexual abuse center, 300 children (22.6%) were less than 5 years old. Preschool victims' gender, race, and frequency of positive physical findings were similar to the older child victims; 17.7% were male, 75.7% were black, positive physical findings were present in 37.7%. The children <5 years old were more likely than older children to be abused by relatives (53.4% vs 39.1%) and less likely to be abused by strangers (3.7% vs 17.7%) (p<.001). Unlike older victims whose abuse often involved attempted or completed vaginal, anal or orogenital penetration (76%), preschool victims less frequently presented with these complaints (40%), and more frequently with fondling (35.3% vs 14.3%), and suspicions of abuse without clear disclosure (24.7% vs 9.7%) (p<.001).

Victims with suspicions of abuse included: children with anogenital trauma or sexually transmitted diseases (STD); partial disclosure by the child, an adult, or a co-victimized child; or unusual behaviors in the child and/or the suspected abuser. Of these 74 cases, 10 (14%) involved partial disclosure by a co-victimized child and 23 (31%) involved trauma or STD. The proportion of cases presenting as suspicions decreased with age up to age 5 y.o.; 69% of victims <2 y.o., 43% of victims 2.0 to 2.9 y.o., and only 6% of victims 3.0 to 4.9 y.o. presented as suspicions. However, 9.7% of children ≥5 y.o. presented with suspicions of abuse.

Preschool aged children <3 y.o. evaluated for sexual abuse often present with suspicions of abuse, since many can not and others are reluctant to disclose abuse. Some may not be actual victims of abuse. Preschool aged children ≥3 y.o. present with complaints of abuse which are more like that of older children.

Poster No. 51
Child Sexual Abuse by Uncles

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No study to date has focused on uncles who sexually abuse their nieces and nephews. The purpose of this study was to describe the characteristics of abuse by uncles and consider risks related to these specific features.

Uncles were the abusers of 71 (5.4%) of 1327 children under age 15 years evaluated at a sexual abuse center. Gender, race, and age distribution were similar to all child victims; 17% were male, 83% were black, mean age was 7.5 years. Most abuse involved attempted or completed vaginal, anal or orogenital penetration (65%) and involved single episodes (62%). Uncles' victims reported less violence (20% vs 33%, p<.01), but had no difference in physical findings (45% vs 36%, p>.05) when compared to victims of other abusers.

Most abusers (87%) were maternal uncles. Maternal uncles may have had more access to victims than paternal uncles since 73% of victims lived in single parent households headed by mothers. Half (49%) of the abusers were young adults 18-24 y.o., 21% were teens 13-17 y.o., 25% were ≥25 y.o., and only 4% were preteens. The abuse typically occurred while the abuser was living in the child's home (41%), or while the child was visiting the abuser's home (39%). Less frequently abuse occurred when the abuser visited the child's home (11%). Of six abuse incidents occurring during babysitting (8%), five involved teenaged uncles abusing younger girls. Twelve uncles (17%) were known to have previously abused other children, yet still were allowed an opportunity to abuse their nieces.

Uncles frequently engaged their victims through non-violent means, abusing children while they visited or lived in the uncles' homes. Recognition that teenaged uncles who are babysitting, and uncles with prior histories of abusing children may pose particular risks to their nieces may aid preventative efforts.

Poster No. 52
Prevalence and Recognition of Potential Growth Failure in a Pediatric Emergency Department

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Emergency Departments (ED) serving an urban pediatric pop. are increasingly the site of episodic primary care. Since monitoring of growth is a central aspect of primary care and an important indicator of overall health, we wished to determine the prevalence of potential growth failure (PGF) and its recognition in children < 6 y presenting to our ED. Triage staff, blind to the research questions and trained in the use of standard scales and stadiometers, measured 1597 (84%) non-emergent children of all 1906 children seen during a one month monitoring period. Using NCHS growth curve standards, we found that 8.3%, 6.6%, and 3.3% of measured children fell below the **5th centile** for height (H), weight (W), or expected weight for height (WH), for a total of 183 children with PGF (11.5% of those measured). Using a more stringent cut-off of <2SD below the mean, 5.8%, 4.8%, 2.4% of children had PGF for H, W, or WH, respectively, for a total of 140 with PGF (8.8% of those measured). ED charts and medical records were reviewed to classify the 183 children with PGF as: recognized by ED staff (8), previously recognized (15), premature (23), dehydrated (6), or having a chronic illnesses which could be associated with PGF (19). After excluding these cases, 112 (61%) children remained unrecognized and unexplained. Among the 140 children reaching the more stringent criteria for PGF, 78 (56%) remained unrecognized and unexplained. PGF is a common (5-7 cases daily) but frequently missed diagnosis in children < 6 y presenting to an urban ED (only 8 cases were recognized over a one month period). Since the ED may be the principal source of primary care for many children, routine screening for PGF in the ED should be considered.

Poster No. 53
Prehospital Management of Asthma Requiring Hospitalization

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The morbidity and mortality of pediatric asthma is increasing. In Boston, asthma accounts for up to 10% of pediatric Emergency Medical System (EMS) transports. In July of 1990 a standing order was written permitting Paramedic (ALS) providers to deliver nebulized albuterol in pediatric patients with significant bronchospasm. The system is dependent on accurate field evaluation by Basic Life Support providers (BLS) who subsequently request ALS assistance. To test the hypothesis that improvement in BLS assessment is needed to improve the quality of care, the EMS management of asthma requiring hospitalization (ARH) to the BCH PICU (ARH-I) and to the BCH ward (ARH-W) was reviewed. A retrospective chart review of ARH-I from 7/1/90 to 11/30/91 and ARH-W from 6/1/91 to 11/30/91 was performed. We identified 12 patients with ARH-I and 15 patients with ARH-W who were transported by EMS.

Only 58% of ARH-I (7/12) and 66% of ARH-W (10/15) had a physical exam marker of asthma severity noted on the EMS record. Sixteen percent (2/12) of ARH-I and 0% (0/15) of ARH-W received albuterol in the field; the two treated patients were the only ones transported by ALS. Twenty-five percent of ARH-I (3/12) and 27% of ARH-W (4/15) did not receive oxygen. Five patients with ARH-I and 3 patients with ARH-W were hypoxic (O2 sat < 94%, range 80-93%) at ER presentation. None of these patients (O/8) had received albuterol. One of the eight hypoxic patients did not receive oxygen.

Our data demonstrates that prehospital assessment and management of pediatric asthma needs improvement. More study is required to determine if intensified BLS provider education and BLS delivery of albuterol in the field would improve prehospital management of pediatric asthma.

Poster No. 54
The Aftermath of Sexual Abuse (SA) Reporting

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We studied parents' perceptions of the consequences of reporting SA. *Results:* We interviewed parents/guardians of 51/107 (48%) children whom we had evaluated for SA from 10/39 thru 9/90. 80% of the children were female; 47% were <5 y old. Evaluation was a response to a child's outcry in 18 (35%) cases, to physical symptoms in 11 (22%) and to abnormal behavior in 7 (14%) cases. Direct outcry was rare when the offender was a family member (3/15 v 14/34; p<0.001) As a consequence of reporting, 28% of children changed homes, 21% changed schools, and 24% had a change in caretaker at home. 43% of parents reported improvement in their child's behavior. Improved behavior was associated with counseling (p=0.002), with charges being pressed (p=0.07) and with conviction of the perpetrator (p=0.007), and was not associated with the relationship of the perpetrator to the child, or with changes in home, school, or caretakers. 47% of parents felt lost during the SA evaluation. Parents who had not reported the SA themselves were more likely to feel lost (p=0.01). 20% of parents said that, before reporting again, they would consult their own lawyer. 62% said that at least one part of the evaluation process was harmful for their child. All but 1 would report SA again.

Conclusions: Reporting SA leads to medical and legal intervention and to social changes which parents do not always perceive as good for children. Many parents felt their interests and rights were overlooked during the evaluation.

Poster No. 55

Appropriate Use of Computed Tomography in the Emergency Room

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Central nervous system (CNS) emergencies are frequently evaluated in the emergency room (ER). A timely accurate diagnosis must be made, since delay in treatment may result in increased morbidity or mortality. With the medical-legal ramifications of "missed" diagnosis, there appears to be an increased emergent use of computed tomography (CT) for minor CNS insults or complaints. The medical records of all patients evaluated in the ER at Arkansas Children's Hospital who underwent emergency CT from June 1990-June 1991 were reviewed. The patients were categorized into either shunt malfunction, trauma, or other CNS complaint. Sixty-seven patients with possible VP shunt malfunction, 143 trauma patients and 102 "other" patients had 316 emergency CT scans. There were 53 abnormal CT scans. Twenty-four of those patients had an abnormal neurological exam, 9 were normal and 20 had no documented neurological exam. Of the 263 normal scans, only 11 patients had an abnormal neurological exam, 154 were normal and 98 had an undocumented or incomplete neurological exam. No patient with a normal neurological exam and an abnormal CT required surgical intervention. A total of 118 ER records had an undocumented or incomplete neurological examination (37%). A thorough, documented neurological examination is imperative when evaluating a pediatric patient with a CNS complaint. Criteria for more appropriate use of emergent CT scanning based on a good history and neurological examination could be developed.

Poster No. 56

A Follow-up Study of Behavior Problems Associated With Child Sexual Abuse

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The nature of behavior problems associated with child sexual abuse is unclear due to the lack of controlled longitudinal studies using standardized measures. The Child Behavior Checklist (CBC) was administered to parents of 132 prepubertal children referred for evaluation of sexual abuse and 80 children matched on age and gender, but with no history of sexual abuse. A follow-up CBC was completed 4 months later by 48% of parents of sexually abused children.

Sexually abused children had significantly more behavior problems than comparison group children (p<.0005), including depression, aggression, sleep and somatic complaints, delinquency, hyperactivity and sexual problems. At follow-up, there was minimal, but significant improvement in overall behavior (p<.04), although sexually abused children still exhibited more problems than comparison children. The improvement was not related to whether a child disclosed abuse, abnormal physical findings, characteristics of the abuse, child's age or participation in therapy.

In summary, sexually abused children displayed a range of behavior problems, that persisted over several months, and were not generally specific to sexual abuse. Pediatricians should ensure these children receive the services they need.

Poster No. 57

Sexual Abuse: Developmental Differences in Psychological Adjustment

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Developmental differences in behavioral adjustment and self-perception were examined in 44 low income preschool and school age children referred for evaluation of sexual abuse and 41 comparison children with no history of sexual abuse, matched on age and gender and from a similar socioeconomic background. Children in the sexual abuse group were rated by their parents as having more internalizing and externalizing problems than comparison children ($p < .01$) on the Child Behavior Checklist. When children rated their self-competence and social acceptance, there were no group differences between abused and non-abused children. However, there was significant within group variation among children in the sexual abuse group. Cognitive competence, physical competence, and social acceptance were higher among younger children than among the older children ($p < .01$). There were no age differences in self perception among children in the comparison group. Preschool children may not be aware of the social sanctions against sexualized behavior and may not recognize the potential harm associated with abuse. The results suggest that not only does the psychological functioning of abused children vary by the child's developmental level, but that clinicians need to consider the developmental coping strategies available to children and recognize that children and parents may differ in their perceptions.

Poster No. 58

Body Weight and Hymenal Opening Size in Prepubertal Suspected Sexual Abuse Victims

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Of 976 prepubertal female suspected sexual abuse victims, 95 (9.73%) were designated as "overweight" (OW), defined as weight at least 3 percentiles greater than height on standardized growth curves. Medical findings of the OW group were compared with those of an age-matched (by mean and distribution) group (CO) of 331 patients. Genital examinations were conducted with a photocolposcope and hymenal opening measurements were made with a standardized technique using photographs of the patients in the supine position with labial traction.

The OW and CO groups did not differ in frequency of penile contact, vaginal contact, penile-vaginal contact, penetration or ejaculation. The CO group had a higher frequency of hand-vaginal contact (29.61% vs. 17.89%; $p = 0.0327$) and pain with contact (25.98% vs. 14.74%; $p = 0.0322$). The OW group had a higher frequency of history of UTI (13.68% vs. 6.34%; $p = 0.0347$) and vaginitis (30.53% vs. 19.03%; $p = 0.0239$). Physical evidence of anogenital trauma was present in 36.84% of the OW patients and in 28.10% of the CO group (N.S.: $p = 0.13$). The mean transverse hymenal diameters were nearly identical in the two groups (OW: 4.9 mm.; CO: 4.8 mm.). The OW group had a greater mean vertical hymenal diameter than the CO group (6.7 mm. vs. 5.8 mm; $p = 0.0099$).

The findings validate the clinical observation that obese patients frequently have vertically elongated hymenal openings. Body weight should be considered as another non-trauma factor which, along with congenital variability, patient relaxation, and examination position and technique, influences the dimensions of the hymenal opening.

Poster No. 59

The Routine Use of Radiography and Arterial Blood Gases (ABGS) in the Evaluation of Blunt Trauma (BT) in Children

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Trauma constitutes the most common cause of death in children over one year of age. The predominant mechanism of major injury is BT. Many emergency departments include chest, cervical spine, pelvic radiographs and ABGs as routine procedures in children with histories suggestive of moderate to severe BT. The purpose of this study was to evaluate the utility of routine radiographs and ABGS in children with BT whose glasgow coma scores (GCS) were 15.

A chart review was conducted over a 12 month period on children seen in BCH Pediatric ED (level 1 trauma center), who were <15 yrs of age and victims of BT. These children were assessed by our trauma team, and had data collected systematically and prospectively. 75 children with BT and normal GCS were identified; mean Modified Injury Severity Score = 4.0; mean age 6.4 years (5 mths-14 yrs). Mechanism of injuries included pedestrian MVA (59%), falls (24%) passenger MVA (13%), and other (4%). 33 of the 75 had an abnormal sign or symptom noted on physical exam (eg. pain on palpation, gross deformity of an extremity), of which 22 had a positive XRAY finding (eg: femur or pelvic fx). In contrast, the 42 without physical findings or complaints all had negative routine radiographs ($p. < 001$, sensitivity of positive sign/symptoms 100%, false negatives 0%). 59 had ABGS - five (6%) were abnormal - all had either an obvious significant fracture or fall from >15 feet.

We suggest that careful observation and repeat examinations by trained clinicians can select a group of children at low risk for occult injuries. This may lead to a more efficient and cost effective management of the pediatric trauma patient.

Poster No. 60

Parents' Understanding of Their Child's Diagnosis After A Visit to the Emergency Department

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Using exit interviews, we determined parent understanding of their child's diagnosis (Dx), medication (Rx), and follow-up (F/U) after a visit to the ED.

Over 2 weeks, 159 parents were interviewed. Exclusion criteria: language other than Spanish or English; admission; trauma; child abuse; or primary psychiatric Dx.

Neither language nor satisfaction, (reported in 93%), was associated with ability to state the Dx correctly ($P>0.10$). 75% (88/117) of parents of children given a single Dx stated it correctly; 55% (23/42) of parents of children given multiple Dx stated them all correctly ($P=0.013$). If a single Rx was prescribed, 30% (20/67) of parents knew its name, while only 13% (4/31) knew all names of multiple Rx ($P=0.070$). Of those given a single Rx, 51% (34/67) knew how to administer it, but only 10% (3/31) knew how to administer multiple Rx ($P<0.001$). Similarly, 58% (46/79) of parents given a single appointment knew the date and place of their child's F/U, while only 16% (3/19) given multiple appointments knew all dates and locations ($P=0.001$). These data suggest that despite high parental satisfaction and knowledge of Dx, parents do not understand their child's Rx and F/U.

Poster No. 61
The Potential Impact of Using an Urban Emergency Department (ED) to Immunize Pre-School Children

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Missed opportunities to vaccinate contribute greatly to poor immunization rates in urban pre-school children. The U.S. Surgeon General has recommended using the ED to provide missing vaccinations. To evaluate the efficacy of this approach, immunization and lead screening rates; primary care clinics (PCC) and ED visits were reviewed for the first 24 months of life in 100 children who had at least one ED and three other visits to two affiliated PCCs by age two.

There were no significant differences between the two PCCs studied. The average number of well visits were 6 ± 2. By one year of life, 71% received 3 DPTs; by 2 years 83% received MMR, 59% HIB, 62% 4 DPTs and 47% were screened for lead. This group also averaged 6 ± 4 visits to the ED (3.7 visits by one year of age). Vaccination and lead screening could have been done in 67% of ED visits and if offered would have increased rates for 3 DPTs (to 87%, $p<.009$), MMR (to 97%, $p<.002$), HIB (to 86%, $p<.001$) and lead screening (to 88%, $p<.001$) as compared to rates achieved in the PCC alone. In an urban children's hospital routine vaccination and lead screening in the ED may improve health care.

Poster No. 62
The Efficacy of Parent Education in the Pediatric Emergency Department

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Little data are available about the efficacy of education in the acute care setting. We examined the effectiveness of parent education in the pediatric emergency department (PED) in a prospective study using a teaching program (TP) based on a fever model. Patients presenting to the PED with a fever were eligible; their parents were randomly assigned to one of three groups. Group A (GpA $n=26$) was the control. Group B (GpB $n=48$) received a standardized TP with both oral instruction and printed materials (PM). Group C (GpC $n=25$) received only PM. Effectiveness of the TP was evaluated by a pre-test (PreT) and post-test (PosT) at the beginning and end of the PED visit, and by telephone survey 1-4 days later, and again 2-4 months later (GpA and GpB only). Results were analyzed using ANOVA, paired t test, chi square and Fisher's exact test.

Sociodemographic variables and PreT scores were similar for all groups. Using the change from PreT to PosT score as a measure of acquired knowledge, GpB was the only one to have a significant increase in score (13 total questions, mean changes in score: Gp A: 0.4±1.1, GpB: 2.0±1.7 $p<.05$, Gp C: 0.5±1.2). 73% of parents enrolled completed the follow-up at 2-4 months. GpB had a persistent increase in PosT score at this visit (1.7±1.8, $p<.05$), demonstrating that the TP did result in long term retention of information. In addition, 95% of parents in GpB found the TP helpful. We found that parents were enthusiastic about our TP in the PED, and that they did acquire and retain knowledge.

Poster No. 63
Factors Associated with Non-Medical Admissions of Children From the Emergency Department

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To better understand the variables impacting on the decision to admit children from the ED, a multi-center prospective questionnaire survey was completed by the admitting physician for all ED admissions. The survey recorded demographic data, insurance status, primary care provider {PCP}, admitting diagnoses and reason for admission. The reason for admission was noted as being strictly medical {MedAd} or non-medical {NMedAd} (medical/surgical illness that could have been managed at home, or purely social admissions). Group differences were analyzed by t-test or chi-square analysis where appropriate.

Over the three month study period there were 4318 ED admissions at 5 institutions of which 185 (4%) were NMedAd. No age or sex differences were found between MedAd and NMedAd. NMedAd were more likely than MedAd to have medical assistance ($p<.001$), no PCP ($p<.001$) or a PCP in a clinic setting ($p<.001$). NMedAd were more likely than MedAd to occur after 5 P.M. ($p<.004$). 'After hours' admissions were also more likely to occur for children with no PCP ($p<.025$) or a clinic PCP ($p<.008$).

These data suggest that children with lower socioeconomic status and limited primary care resources are more likely to be admitted for non-medical reasons than children with commercial insurance or a private physician.

Poster No. 64
The Incidence of Acute Infections in HIV Positive Children Presenting to the Emergency Department

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Forty-three non-hemophiliac confirmed HIV positive children followed by the Children's Hospital AIDS Program made 184 visits to the Children's Emergency Department (ED) during 1988 and 1989. The mean age was 30±28 months (median 25 months, mode 10 months), with a range from 2 days to 19 yrs. CD4 counts from within 6 months of the visit were available in 87% and were low enough to require PCP prophylaxis under current guidelines in 52%. Chief complaints included fever in 50%, respiratory symptoms in 21%, and gastrointestinal symptoms in 8%. The ED discharge diagnoses included fever/possible sepsis in 25%, pneumonia in 17%, otitis media in 9%, URI or viral syndrome in 9%, and other lower respiratory infections in 5%. Overall an acute infection was identified at 62% of visits. Of these 33% were judged serious. A total of 92 blood cultures were drawn: 8 grew the following organisms: *S. pneumoniae* (3), *S. faecalis* (2), *E. coli* (1), *T. glabrata* (1), and *Staphylococcus* non-aureus (1, a contaminant). 53% of patient encounters resulted in hospitalization. 12 patients with a diagnosis of fever/possible sepsis were discharged home, 7 with IM ceftriaxone (1 had *S. pneumoniae* bacteremia), 2 with oral antibiotics, 2 with no antibiotics given in the ED (1 with *S. faecalis* CVL infection treated by home I.V. therapy), and 1 with an unknown antibiotic. None of these patients required admission in the following 3 days. Patients with a WBC count of >15,000/mm were more likely to be hospitalized (87% vs. 62%, $p<0.01$) though the WBC was not helpful in identifying patients with bacteremia or serious infections. The mean temperature of admitted patients was higher (38.7° C vs. 37.9° C, $p<0.01$). We conclude that: (1) HIV infected children utilize the ED mostly for acute infections; (2) these infections are often serious, and (3) many can be managed on an ambulatory basis.

Poster No. 65
Application of Minimum Threshold Criteria for Reporting Child Abuse From Health Care Settings

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Although it is estimated that hospital personnel report to child protective service agencies (CPSAs) only two-thirds of the child abuse cases they identify, such estimates are based on implicit, ambiguous criteria for reportable abuse episodes and may be invalid. To find whether hospital personnel consistently report to CPSAs episodes that most clinicians would agree constitute abuse, we developed specific minimum threshold criteria for reportable neglect (N), physical abuse (PA), and sexual abuse (SA). We then applied these criteria in an audit of 62 randomly sampled charts of children reported by hospital-based clinicians to CPSAs between 1990 and 1991. The mean age of the reported children was 6.0±5.7 yrs. Thirty-four (55%) were boys. Twenty-nine children (47%) were reported for N, 19 (31%) for PA, and 14 (23%) for SA. The time elapsed from first hospital visit to the index abuse report averaged 4.3 yrs for the 52 children seen previously. Hospital records contained 20 earlier reports to CPSAs concerning suspected abuse of 12 of the 62 children and 4 episodes involving 3 children that met our criteria but had not been reported. Thus, application of explicit criteria resulted in the finding that 20 (83%) of 24 suspected abuse episodes were actually reported to CPSAs (95% confidence interval: 62.6% to 95.2%). We conclude that use of ambiguous reporting criteria underestimates hospital personnel's compliance with child abuse reporting laws. Specific criteria for reporting suspected abuse are a prerequisite to valid, reliable study of clinicians' decision-making behavior, may reduce bias in reporting decisions, and may facilitate hospitals' quality assurance activities.

Poster No. 66
Gunshot Wounds in an Urban Children's Hospital

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Gunshot wounds (GSW) are an increasing portion of the burden of violence experienced by urban youth. To define risk factors for intentional GSW and to help plan a violence prevention program, we surveyed all firearm injuries in a busy (4400 visits/month) urban children's hospital Emergency Department from April to December 1991. We abstracted medical record information on demographics, injury circumstances, and clinical course. Intentionality was assessed by whether the weapon was discharged purposely at the time of firing.

Results: Of 96 children presenting with GSW, 61 (65%) were admitted and 23 required surgery; 19 (20%) had an ISS >15, 11 (12%) were permanently disabled and 12 (13%) died. Drug screens were only done on 25 (26%) patients, but were positive in 13 (52%). The 96 victims were overwhelmingly black (91%), male (85%), and >12 years old (88%). Where weapon type was known (N=78), handguns accounted for 76% of injuries. GSW occurred on streets or public locations in 56 (71%) of the 79 with identifiable locations. GSW were intentional in 62 (65%) and of indeterminant intent in 19 (20%). The mean age of intentional GSW victims was significantly greater than that of unintentional victims (15 vs 13 years, p=.02). For intentional compared to unintentional GSW, the odds ratio for black race was 26.2 (95% CI 4.6, 149.0), for low SES was 4.8 (1.2, 18.9), and for street/public locations was 5.6 (1.4, 22.4). The association with black race was confounded by SES. Cases with indeterminant intent were sociodemographically similar to intentional cases.

Conclusions: Nonfatal GSW consume substantial medical resources and result in considerable morbidity, disproportionately affecting adolescent males. The identified characteristics of intentional GSW victims will enable targeted violence prevention programs.

Poster No. 67
Efficacy of Magnesium Citrate in Pediatric Ingestions

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The paucity of pediatric data concerning the use of cathartics in toxic ingestions results not only in the lack of a uniform approach but also the potential for unsafe, ineffective treatment practices. This study investigates the efficacy of magnesium citrate (MgC) in reducing gastrointestinal transit time in children who present with toxic ingestions. Children, aged 1 mo. to <6 yrs, who presented to the emergency department for poisonings were randomized to receive activated charcoal (AC) and: 1) *water,* 2) *MgC 4cc/kg,* 3) *MgC 6cc/kg* or 4) *MgC 8cc/kg.* The onset and frequency of charcoal stools were noted by follow-up phone calls within 48 hours. 56 children, mean age 25 mos., were entered into the study. Mean time to first charcoal stool was: 1) *17.1 hrs (N=7, range 5-24),* 2) *15.2 hrs (N=16, range 4-39),* 3) *15.7 hrs (N=16, range 6-27)* and 4) *11.9 hrs (N=17, range 3-22).* ANOVA revealed no statistically significant differences between groups in onset or frequency of charcoal stooling. Power analysis revealed the ability to detect, if it existed, a difference of 8 hours or more between groups with 90% confidence. A trend was seen for more rapid onset of charcoal stooling with the highest dose of cathartic. No clinically significant adverse effects were reported. We conclude: 1) the time of onset of charcoal stools in childhood poisoning is highly variable 2) larger doses of MgC than curently recommended may be required to achieve a cathartic effect in children. Further study is required.

Poster No. 68
Decreasing Inappropriate ED Use

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The use of emergency departments (ED) for minor medical concerns greatly increases the cost of medical care and may interfere with the provision of comprehensive primary care (PC), negatively impacting the patient's overall health. Interventions designed to decrease such "inappropriate" use of ED have had mixed success.

Children presenting to the ED and triaged as non-urgent were randomly assigned to one of three groups: Control-no intervention given; Track 1-a non-professional research assistant spoke with the parent about their decision to come to the ED for this problem, their usual source of PC, and the importance of PC, and then assisted them in arranging an appointment with a PC provider; Track 2-a nurse or social worker spoke with the parent about the same issues and, in addition, provided "case management" for the family over the next 3 months.

Three months after the index ED visit, 29%, 16%, & 47% of Track 1, 2, and Control returned for a second ED visit (p=.002) and 29%, 24% & 41% returned 8 months later (p<.05).

"Inappropriate" ED visits can be significantly decreased by patient education and primary care referral.

Poster No. 69
Decision Rules for Predicting Undervaccination of Preschool-Age Emergency Department (ED) Patients

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Objective- To develop and test rules to predict vaccination status (VS) among preschool age ED patients. *Design-* Cross-sectional survey. Guardians of ED patients were asked about their child's VS, socioeconomic status, child care use, household composition, health insurance, source of primary care, and ED utilization. Physicians' office charts were reviewed to verify VS. Decision rules were developed using recursive partitioning. *Setting-* A pediatric ED in an urban teaching hospital in Rochester, NY. *Subjects-* 605 children, ages 4 to 48 months, who were residents of Monroe County, NY were consecutively enrolled. Subsequently, a replication sample of 716 ED patients ages 6 to 36 months was enrolled. *Results-* Four rules produced in this way varied in number of questions, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV):

Original Subjects				Validation Group				# of Questions
Sens.	Spec.	PPV	NPV	Sens.	Spec.	PPV	NPV	
.40	.95	.69	.85	.46	.93	.68	.85	2
.42	.92	.60	.85	.49	.92	.66	.85	1
.81	.59	.36	.92	.72	.61	.37	.87	4
.88	.53	.35	.94	.75	.56	.35	.88	6

Questions comprising these rules included maternal report on child's VS, timing of the most recent doctor visit, maternal age, household size, and inner-city residence.

Conclusions- Simple decision rules can be used to identify patients most likely to be undervaccinated.

EPIDEMIOLOGY AND PREVENTION

Poster No. 70
Immunization Status and Birth Order

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In order to determine whether an association exists between immunization status and birth order, immunization information on 446 families attending an urban hospital pediatric clinic was examined. Median ages at which first and second-born siblings were immunized with DTP and MMR were compared. OPV and Hib administration were not examined (OPV was given concurrently with DTP; recommendations for age of administration of Hib changed several times during the study period). The Wilcoxin Matched-Pairs Signed Rank Test was used to determine whether birth order and age at each immunization was related. DTP1, DTP2, and DTP3 were found on average to have been administered 5 (Z=3.1, p=.002), 10 (Z=4.5, p<.0001), and 20 (Z=.4.0, p=.0001) days later respectively to second-borns than to their first-born siblings. No significant differences were found regarding time of administration of MMR1 and DTP4.

The McNemar Test was used to compare percentages of first and second-born siblings up to date on all immunizations at each month of age. Significantly fewer second-borns than first-borns were fully immunized at 5 months of age (χ^2=17.9, p<.0001) and at each subsequent monthly interval through 11 months of age. Interventions should be targeted toward second-borns to reduce their heightened risk of immunization delay in the first year of life.

Poster No. 71
A Population at Risk: Children in Foster Care

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Background: There is a paucity of recent data on health problems of children in foster care.

Objective: To assess the prevalence of medical, psychological, and educational problems of children in foster care.

Design: Retrospective medical chart review of a random sample of children attending a Foster Care Clinic (FCC).

Setting: Monroe County, New York, in which the Pediatric FCC provides primary care to 90% of children in foster care.

Subjects: In 1988, 710 of the 805 children in home-based foster care were patients of the FCC. We reviewed the medical charts of a random sample of 33% (N=234).

Results: The mean age was 10.1 years (SD=5.5); 44% were black. The median length of stay in foster care was 2.6 years (range 0.1 to 18.7 years). 65% had more than one foster care placement; 11% had more than five placements. Most children had multiple reasons for placement, including parental substance abuse (27%), neglect (69%), physical abuse (18%), sexual abuse (15%), and childhood behavioral problems (17%). 101 patients (43%) had a major chronic health problem; these included developmental delay (14%), speech delay (11%), asthma (9%), and failure to thrive (6%). Of children more than 3 years of age, 65 (31%) had a specific psychiatric diagnosis, including attention deficit disorder (18%), affective disorder (4%), and a specific behavioral disorder (17%). 45% of school-age children were enrolled in specific education.

Conclusions: Children in foster care have a markedly higher rate of medical, psychiatric, and educational problems than the general pediatric population. Optimal management should include a multidisciplinary evaluation following initial placement, and ongoing primary care by pediatricians, mental health workers, educators and social workers.

Poster No. 72
Injuries to Children Involving Home Exercise Equipment

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In 1990, exercise equipment related injuries were responsible for an estimated 25,269 emergency department visits, representing a 400% increase since 1982. Children younger than 15 years of age were involved in over 50% of these cases. Despite the growing incidence of these injuries, the medical literature has yet to address this problem. In this study, case reports collected by the US Consumer Product Safety Commission (CPSC) between 1981 and 1991 are reviewed in order to evaluate injuries associated with home exercise equipment.

87 cases were found to involve children, 64 were boys and 23 were girls. The children ranged in age from 7 months to 16 years, with 64% ≤5y.o. Additionally, 40% of the deaths and 75% of injuries requiring hospitalization involved children ≤5y.o. In over 80% of the cases, children were playing alone and unsupervised when the injury occurred. The types of equipment most commonly associated with injury were stationary bicycles and jump ropes. 55% of the injuries were related to stationary bicycles. Of these, amputation was the most frequent type of injury (65%), typically resulting from entrapment of fingers or toes in the chain and sprocket assembly (85%). Jump rope injuries accounted for 25% of the case reports, of which 64% resulted in death. These deaths comprise 70% of all deaths reported in the CPSC data regarding exercise equipment.

CPSC case reports are obtained for only a sample of the estimated number of injuries associated with exercise equipment occurring annually. This sample, partially based on surveillance data (NEISS reports), is expected to represent types and patterns of injury. Injuries to children involving home exercise equipment are frequent and potentially severe, but almost entirely preventable through product modification and parental supervision. Pediatricians need to play an active role in educating parents and the community about the potential hazards that exercise equipment presents to young children.

Poster No. 73
Illness Severity and Adjustment

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Many interrelated factors contribute to the successful adjustment of children with a chronic physical illness. We have previously reported the powerful effects of the family's interpersonal functioning, of the mother's locus of control orientation, and of the child's temperament.

Parents of 162 children and adolescents with an idiopathic seizure disorder, cerebral palsy, spina bifida, or another condition with orthopedic involvement reported the # of school days missed, the # of doctor visits, and the # of hospitalizations as a result of the child's illness, and rated their impressions of the illness severity. Using multiple regression analyses, we assessed the association of the relatively objective indicators and of the parent's subjective ratings of severity with assessments of the child's adjustment.

Both objective indicators of illness severity and parents' ratings were directly and significantly associated with parents' ratings of children's adjustment (r=.23 and .40 respectively, p<.01). When age, gender, intelligence, socioeconomic status and illness duration were statistically controlled, parents' subjective ratings were more strongly associated with adjustment than were the objective indicators (R^2=.36, p<.001). Parents' impressions about the severity of their child's illness appear to be at least as important as more objective indicators of illness severity to children's successful adjustment.

Poster No. 74
Screening for Childhood Lead Poisoning: A Decision Analysis

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The 1991 CDC guidelines recommend universal blood lead (BPb) screening for children under 6 yrs of age. Specimens obtained by venipuncture (VP) are preferred because of potential contamination using capillary sampling (CS). Repeat screening by VP is recommended when the initial result by CS is ≥ 0.72 µmol/L (15 µg/dL). However, obtaining specimens using VP is more difficult compared to CS, and therefore universal screening using VP is not a widely used strategy. We used decision analysis to compare three screening strategies: VP as the initial screen [VENOUS]; CS as the initial screen, with VP confirmation if BPb is ≥ 0.72 µmol/L [CAP]; VP for high risk children/CS for low risk children as the initial screen, with VP confirmation if BPb is ≥0.72 µmol/L [STRATIFY]. Using data from the literature and hospital costs we estimated the average cost of screening by each strategy. Baseline variables included: costs of BPb determination ($16), obtaining sample by VP ($3) and CS ($3); contamination rate by CS (22%); and prevalence of BPb ≥ 0.72 µmol/L (17%). Results were as follows:

Strategy	Cost/Child
VENOUS	$29
CAP	$35
STRATIFY	$34

Sensitivity analysis demonstrated that VENOUS remained the least expensive screening strategy for reasonable changes in all variables. Even when the prevalence of BPb ≥ 0.72 µmol/L is 1%, VENOUS remains the least expensive strategy. CAP becomes a less expensive strategy than VENOUS only when the cost of VP exceeds CS by more than $7 per sample.

We conclude that universal BPb screening by VP is the least expensive screening strategy for childhood lead poisoning. With universal screening of U.S. children under age 6, an annual savings of $80 million to $96 million could be realized using the VENOUS strategy compared to the STRATIFY or CAP strategies

Poster No. 75

Majority of Children in an Inner-City Clinic Population Have Lead Levels Exceeding the Center for Disease Control Revised Intervention Threshold

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Because of increasing evidence regarding the harmful effects of low-level lead exposure, on October 7, 1991, the Center for Disease Control revised the previous intervention level of 25 μg/dL (1.21 μmol/L) downwards to 10 μg/dL (0.48 μmol/L). The purpose of our study was to determine the proportion of children in our inner-city pediatric clinic who have venous blood lead levels above the new threshold.

The study population consisted of 105 consecutive patients ages 10 months to 6 years who were seen in our well-child clinic and were due for routine blood lead screening. None of these children were previously known or suspected to have lead poisoning. Results of the 105 venous screens are as follows:

Lead Level > μg/dL: (μmol/L):	0-9 (0-0.43)	10-14 (0.48-0.68)	15-19 (0.72-0.92)	20 (0.97)
Number of patients (n = 105)	25	35	22	23

These results indicate that 76% of the children screened had levels in excess of the new threshold, and will require additional pediatric care. Under the old guidelines, only 8.6% of the same children had results requiring intervention. The ubiquitousness of lead levels above the new threshold will necessitate extraordinary effort and financial commitment on the part of both the pediatric profession and the community as a whole.

Poster No. 76

Health Status of Children of Cambodian Refugees

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Little is known about the health of US born children of Cambodian refugees. We undertook a longitudinal study of newborns born to Cambodian women obtaining prenatal care at a neighborhood health center in Revere, MA.

We assessed demographic conditions, social support and depressive symptoms during pregnancy (n = 73). We reviewed medical records through 18 months to identify birth outcomes, physiologic health (e.g, growth, Hct, FEP), and health care use (ER visits, immunization rates). We performed in-person assessments at 9 (n = 53) and 18-24 months (n = 44) to assess the home environment (HOME and NCAST) and development (Bayley at 9 m., preschool language scale at 18-24 m.)

Half of mothers reported family income under $10,000. Forty per cent were illiterate (English or Khmer). Over half (51%) of pregnancies were undesired. 58% of women reported systems above the threshold for clinical depression. Despite these risks, Cambodian children showed few adverse findings at 2 years. Indices of growth and iron stores (Hct = 36±4, FEP = 42±14) were near normal; immunization rates approached 100%; Bayley (MDI = 100±14) and preschool language assessments were also normal.

These results suggest that, among users of a comprehensive community based program, early childhood outcomes in this population give hope for successful adaptation to later challenges.

Poster No. 77

Lead Screening Opportunities Missed Among Urban Children

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The 1991 CDC lead guidelines recommend rescreening children with blood lead levels ≥ 10 μg/dl every 3 to 4 months. There is concern that the new guidelines will greatly increase the number of lead tests performed and thus be difficult to implement. Moreover, little data are available about screening rates based on 1985 CDC guidelines. We investigated whether inner-city children ages 9-25 months cared for at one university affiliated, hospital based pediatric clinic were screened annually, whether those not screened had missed opportunities (MO) for lead screening, and whether the 1991 CDC screening guidelines could be accommodated without additional visits.

A group of 746 active patients, ages 0-25 months at clinic enrollment and born between 1988 and 1990, were identified. Clinic visits up to age 25 months were reviewed. A visit between age 9 months and the first lead screen was defined as a MO. Following a lead screen, a MO was defined as any visit 12 or more months later in which a lead test was not obtained. 58% of children were never screened by age 13 months. 20% of children followed for at least one year were never screened by age 25 months. Children never screened had an average of 2.2 MO between ages 9 and 13 months, and 8.9 MO between ages 9 and 25 months. Among those never screened by 25 months, the proportion of MO at well child-care, acute illness, follow-up and administrative visits were 28%, 47%, 11% and 14%, respectively. 63% of children screened had a clinic visit within the next 2 to 5 months indicating that rescreening can be easily accommodated for the majority of children.

These findings indicate that a substantial percentage of at-risk children were not being screened according to conservative guidelines. Many of these children, however, visit frequently enough to accommodate the new CDC guidelines without requiring additional visits exclusively for lead screening.

Poster No. 78

Epidemiology of Injuries in Children From Electrically Operated Garage Doors

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A review of 181 cases of injuries in children from electrically operated garage doors was made to determine injury epidemiology. Of the 181 cases of accidental injury in children aged 0-20 over the period 1980-89, 70 cases (38.7%) resulted in death. Mortality was highest in the 0-10 year age group (67 cases, 96%). Mortality was also higher for males (56 cases, 80%) than for females (14 cases, 20%). The higher rates of garage door injuries and deaths among boys indicates that social and peer influences may contribute to risky games with garage door openers. Even among the reported nonfatal cases of injury from electrically operated garage doors, 26% required hospitalization. Head, neck, and upper trunk injuries accounted for 67% of all injuries. Safety devices are available for electric garage door openers which cause a closing garage door to reverse and open as soon as it contacts an obstacle such as a child's body. Incorporation of such safety devices has been mandated in all new electric garage door installations since 1982, and retrofit kits are available for older models. However, large numbers of garage door openers exist without the safety device, and it has not been established that risk of injury is eliminated even with the safety device incorporated. The prime avenue towards obtaining reduced rates of garage door injuries is widespread public education on the extreme danger posed by electrically operated garage doors, particularly to young children. Educating consumers on safety device retrofit availability, and possibly mandating such retrofits through legislation, are other potential avenues for further reduction in garage door injuries and death.

Poster No. 79

Zapping a Myth: How Safe are Microwave Ovens?

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Microwave ovens are present in 83% of US homes. Although case reports have described burns associated with their use, epidemiologic data are lacking. We reviewed US Consumer Product Safety Commission data from 1986-90 to identify the frequency of burns to children (0-19 yrs). There were an estimated 5160 burns associated with microwave oven (MW) use. The mean age was 7.6 yrs (median, 6 yrs); 25% of burns were to children <36 mo old. 58% involved females. Most MW burns were scalds (95%); 17% of these scalds were from exploding eggs or other food. No MW burn involved a body surface area (BSA) >25% and no patient required hospital admission. We compared MW burns to stove burns. There were an estimated 41198 burns to children associated with stoves; mean age was 5.8 yrs (median, 3 yrs) ($p<.001$ vs MW). 45% of burns were to children <36 mo old. 55% were to males ($p<.001$ vs MW). Most stove burns were thermal (74%); 7% involved a BSA >25% ($p<.001$ vs MW). 5% of children with stove burns required hospital admission ($p<.001$ vs MW). We conclude: 1) burns to children associated with microwave oven use are less frequent and less severe than stove burns; 2) microwave oven burns predominantly affect females; and 3) burn prevention efforts should emphasize the hazards of stoves rather than microwave ovens.

Poster No. 80

Does Home Abatement Lower Blood Lead Levels in Children With Class II Lead Poisoning?

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We studied the effect of home abatement on blood lead levels (PbB) in children from central Massachusetts with Class II poisoning who had not been chelated and whose homes were abated between 1987-90, when stricter abatement guidelines were enacted. 135 children with a mean pre-abatement PbB of 1.24μmol/L were studied; their mean post-abatement PbB (up to 1 year later) with 1.01μmol/L ($p<.001$). This reduction correlated with pre-abatement PbB: all 33 with pre-abatement PbB >1.45μmol/L were lower post-abatement; 65 of 79 (82%) with PbB 0.97-1.45μmol/L were lower. However, in children with pre-abatement PbB <0.97, only 7 of 23 (30%) were lower post-abatement. In fact, in that group, mean PbB rose from 0.77 to 0.96μmol/L ($p<.01$).

We conclude that home abatement was effective in children with PbB >0.97μmol/L, particularly so in those with PbB >1.45μmol/L. This was not the case for children with pre-abatement PbB <0.97μmol/L. Continued improvement in home abatement technology is needed if that strategy is to be effective in achieving the lower PbB levels now mandated in the 1991 CDC guidelines.

Poster No. 81

Childhood Asthma and Poverty: Prevalence, Impact, and Health Services Utilization

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Data from the 1988 National Health Interview Survey on Child Health (NHIS-CH) showed that 4.3% of all children less than 17 years of age have asthma, with poor children demonstrating a slightly greater prevalence than non-poor (4.8 poor *v.* 4.2 non-poor, $p<.05$). This poor non-poor differential was even greater for children less than 6 year old (4.2 poor *v.* 3.1 np). Poor children were more likely to have more than 5 school loss days, and 7 bed-days in the last year due to their asthma ($p<.05$). Measures of health service utilization showed that poor children had 40% fewer doctor visits (3.2 *v.* 5.4, $p<.05$), and had 40% more hospitalizations in the last year (10.6% *v.* 7.4%, $p<.05$). Although over 90% of all children had a usual source of routine and/or sick care, poor children were more likely to receive routine care in a neighborhood health center (15.1% *v.* 4.6%), or hospital based clinic (11.1% *v.* 2.8%) than in a doctors office (67.2% *v.* 91.1%) ($p<.005$); and when sick, were more likely to report an emergency room as a usual source of care (8.1% *v.* 1.7%). Diminished accessibility to appropriate health services for children with asthma has significant impact on morbidity, measured by hospitalization, school loss and bed days. These findings have significant implications for the development of comprehensive models of care and the role that community clinics could play with increased potential funding due to the 1989 Omnibus Reconciliation Act.

Poster No. 82

Epilepsy as a Risk Factor for Submersion Injury in Children

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The purpose of this study was to determine the risk of submersion injury and drowning among children with epilepsy and further define specific risk factors. In a population-based retrospective cohort study we identified and reviewed records of all 0-19 year old residents of King County, Washington who suffered a submersion incident between 1974-1990. Children with epilepsy were compared to those without epilepsy with regard to age, sex, site of incident, supervision, outcome, and presence of pre-existing handicap. Relative risks were determined using population based estimates of epilepsy prevalence.

Of 336 submersions, 21 (6%) occurred among children with epilepsy. Children with epilepsy were more likely to be greater than 5 years old (86% vs 47%, $p=.001$) and more likely to submerge in a bathtub (38% vs 11%, $p=.002$). The relative risk of submersion for children with epilepsy was 47 (95% CI 22-100) in the bathtub and 18.7 (95% CI 9.8-35.6) in the pool. The relative risk of drowning for children with epilepsy was 96 (95% CI 33-275) in the bathtub and 23.4 (95% CI 7.1-77.1) in the pool. These data support an increased risk of submersion and drowning among children with epilepsy.

Poster No. 83

Lead Poisoning in a Non-Inner City Practice

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The acceptable limit for blood Pb has been decreased to 10 mg/dl and universal screening recommended. While Pb poisoning has long been a problem in inner-city populations it has been considered a lesser problem in more affluent populations. We prospectively screened all children 8 to 48 months (× 19 months) to measure the prevalence of elevated Pb in a non-inner city population to determine if screening is indicated in this population.

220 children, 53% male, 62% white, and 74% with private insurance were screened using capillary blood. Using current CDC definitions, the rate of elevated Pb was 17.3%; 12.6% in the children with private insurance (PI) and 34.8% in children receiving medicaid (MA). Black children and children receiving MA were more likely to have elevated Pb levels; when analyzed in a logistic regression only insurance type (MA) was associated with elevated Pb (odds ratio 2.6 95% CI (1.06;6.1). Of the children with elevated Pb 6 of 22 PI children compared with 6 of 16 MA children had at least class IIb Pb poisoning. We conclude that universal Pb screening is a good policy.

Poster No. 84

A Profile of Burn Injuries in an Urban Primary Care Population

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We conducted a survey among mothers bringing their children to our clinic for routine health maintenance or minor acute illness visits in order to establish a profile of pediatric burn injury in an urban setting. Interviews were conducted in English or Spanish with 240 mothers. Sixty-nine percent of mothers were Latin, 16% African-American, 14% white and 1% other. Ninety percent received Medicaid. One hundred mothers (42%) stated that at least one child in their family had been burned. Contact burns accounted for 70% of all burns reported, with the remainder being due to scalds (12%), cigarettes (10%), flame (5%) and unknown (3%). Exposure to a hot iron caused 47% of all contact burns. Other causes of contact burns were cooking appliances (20%), curling irons (13%), radiators and heaters (10%) and other (10%). The majority (59%) of burns received home treatment by parents, relatives or friends; 17% were cared for in the clinic and 16% in the Emergency Department. None required admission to the hospital. The initial treatment provided at home was cold water or ice in only 35% of episodes; other home remedies included creams (20%), toothpaste (12%), and butter (3%). Ironing was a frequently performed chore by mothers in this study; as many as 45% ironed daily, and another 12% ironed three to six times per week. Irons were left to cool in potentially unsafe places most of the time. There was no difference in ironing behavior by mothers reporting burns versus those not reporting burns. In our poor, urban population, the reported likelihood of a burn injury during childhood is high, particularly with respect to contact burns. Increased emphasis on prevention of contact burns in particular populations at high risk should be considered.

Poster No. 85

Effectiveness of a School Based Education Program in Increasing Bicycle Helmet Use and Awareness in School Aged Children

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Objectives. Bicycle related head injuries are an important cause of death and disability, despite the availability of bicycle helmets. The objective of this study was to develop a school program to educate children and parents about head injuries and helmets; improve attitudes toward helmet wearing; make helmets affordable.

Methods. The program was carried out in a mixed income borough in a large urban city, in two high income schools, and two low income schools. Children completed questionnaires before and after. Approximately 1800 observations of bicycling children were made.

Results. Helmet use throughout the borough tripled from 3.4% (1990) to 16% (1991). In high income schools, 93% of children reported owning a bicycle. Reported helmet ownership increased from 17% to 31%. Observed helmet use rose from 4% (1990) to 48% (1991) ($p<0.001$). This was significantly higher than other high income schools which did not receive the program (48% vs. 31%, $p=0.03$).

In low income schools, 80% of children reported owning a bicycle. Reported helmet ownership did not rise (8% vs. 7%). Observed helmet use did not rise significantly between 1990 and 1991 (4% vs. 8%, $p = 0.52$) nor did it differ from other low income schools who did not receive the program (8% vs. 18%, $p = 0.5$).

Conclusions. The program was highly successful in children of high income families, but similar strategies were not successful for children of low income families. We will now focus on developing strategies for children of low income families.

Poster No. 86

Taxicabs and Child Restraint

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Taxicabs are often the primary means of family transportation in urban settings and on vacation. Recent experience with taxicab occupant injuries in children prompted these continuing studies.

State Police and Highway Safety Offices of 51 states (including D.C.) were contacted for child restraint and seatbelt law exemptions and taxicab injury statistics. The Fatal Accident Reporting System provided taxicab occupant mortality by age. Carseat availabilities for 50 taxicab fleets in urban areas of 4 states (DE, MD, NJ, PA) were elicited and Baltimore clinic families were surveyed for taxicab usage.

Thirty-four states (67%) specifically exempt taxicabs from child restraint laws. Of 40 states with seatbelt laws, only 11 (28%) exempt taxicabs. There were 106 taxicab occupant fatalities from 1986-1990, including 8 children. Statewide taxicab injury statistics are not available. Atlantic City, NJ, did report that from 1/89 to 6/91 there were 309 accidents in 250 taxicabs resulting in 1 fatality and 109 occupant injuries, including 4 unrestrained children under 4-years-old. Of the 50 taxicab fleets, only 3 (6%) offered carseats if requested in advance. In Baltimore clinic families, 32 of 40 (80%) did not own a car and 20 (63%) of these families rode in taxicabs with a child less than 3-years-old at least once per month (10) or once per week (10) without restraint.

Conclusions: Data on taxicab occupant injuries are needed. Carseats are rarely available in taxicabs regardless of statutes. Legislation linking carseat availability to taxicab licensure should be considered.

Poster No. 87

Prevalence of Substance Abuse Among Pregnant Women in Utah

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Current information regarding substance abuse in pregnancy stems primarily from studies performed in urban hospitals with minority populations, where reported rates range from 11.5 to 24%. A prevalence study was conducted to determine if these rates are comparable to Utah's primarily caucasian, middle class, urban population. Urine specimens and non-identifiable demographic data were obtained anonymously from women who presented to the maternity wards and subsequently delivered in 1 university and 9 private hospitals over a 19 day period in the summer of 1991. Each urine was screened by enzyme immunoassay for amphetamines (AMPH, cutoff-150 ng/ml), marijuana metabolites (MAR, 20 ng/ml) cocaine metabolites (COC, 150 ng/ml), methadone (METH,150 ng/ml), opiates (OPI, 150 ng/ml), benzodiazepines (BEN, 150 ng/ml), and ethanol (ETH, 10 ng/ml). Of the 792 women screened, the mean age was 26.2 years, 86.1% were caucasian, 62.9% were multi-gravid, and 66.3% had private insurance. The combined prevalence rate of positive urine screens for COC, AMPH, MAR, or ETH was 7.8%, with MAR and ETH detected most frequently. The women positive for one or more of those four drugs did not differ from women negative for those substances in terms of race and parity, but significantly more urine-positive women had Medicaid or no insurance ($p < .01$). Our study produced results similar to a study performed in Rhode Island in 1989, and further confirms that substance abuse during pregnancy is a problem in predominantly white, urban areas, albeit at a lower rate and with a different pattern of drug use than reported in urban hospitals serving minority populations.

Poster No. 88

Prior Risk Status of Postneonatal Deaths: A Total Population Study

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In order to focus efforts to reduce postneonatal (PN) mortality, we examined risk status of infants who died in the PN period in a total population. All PN deaths with birthweights >500 gms. (N = 120) for the city of St. Louis and 32 contiguous census tracts (1985-86) were included. Vital statistics were linked to maternal/infant medical records at the birth, death and transfer hospitals. Causes of death (COD) were obtained from medical record review or autopsy if performed. The major CODs were SIDS (N = 50 42%), Congenital Anomalies (CA N = 25 21%), Prematurity-related (N = 19 16%) and Infection (N = 7 6%). Twenty-four percent (29) of the PN deaths occurred to infants who never left the hospital; 17 (59%) of these were prematurity-related and overall, (89%) of the prematurity-related deaths were never discharged. Of the total 87 discharged, 19 (22%) had active high-risk medical conditions at the time of discharge (CA-14%, BPD-Apnea-6%, Seizures/Hypotonia-2%). Significantly, 31% of infants who died of CA after leaving the hospital did not have a definitive diagnosis at the time of discharge. Of all PN deaths, only 18% left the hospital with active high-risk conditions or were born at a birthweight of <1500 gms. This implies efforts to reduce PN mortality must extend well beyond follow-up of infants discharged at high medical risk.

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

Poster No. 89

Student Clinical Experience and Exam Performance: Are They Related?

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Clinical, affective, technical and cognitive skills are criteria used to evaluate a student's clerkship performance. Clerkships often use standardized NBME shelf tests to assess students' knowledge. We hypothesized that performance on the pediatric shelf test would not be influenced by clerkship patient care experiences. The authors examined the shelf tests in 1987-88, identifying questions in these categories: well baby, neonate, infectious disease, and trauma. In the same year, students (N = 118) recorded all diagnoses and numbers of patients (NOP) seen during their clerkship rotation. Results, using Spearman rank order coefficients, revealed no correlations with NOP seen and their NBME scores in any category. There was also no correlation with the total NOP and the overall NBME score. There was a correlation between NOP and the clinical grade ($p < .0047$) and final grade ($p < .0019$). The NBME scores, as predicted, were not influenced by the students' clinical experiences, contrary to adult learning principles. Clerkship directors should reassess their use of this exam in evaluating students.

Poster No. 90

Evening Appointment Reminder Calling Minimizes Patient 'No Shows' (PNS) and Saves Money

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Fallon Clinic and Fallon Community Health Plan,
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Objective: Decrease PNS, defined as missed appointments and late cancellations (<2 hrs prior to scheduled time).

Methods: Determine effectiveness of evening (5-9 PM) call reminders placed 24-48 hours prior to appointment time made by specially assigned staff.

Results: The PNS rate decreased from 6.4% to 3.9% in our large multi specialty prepaid-FFS group with about 850,000 outpatient visits (16% Pedi) in 1991. The evening calls reached 90% of scheduled patients compared to 40% with daytime phone calling. Cancellations found in advance by the calls give extra same day access. Each filled appointment slot rsults in about a $40 net cost avoidance by making use of otherwise wasted staff and provider time and by saving the average overhead cost of $17 for each PNS. The cost of each reminder call is $0.22 or $3.30 per avoided PNS giving more than 7:1 savings: cost ratio.

Conclusions: Evening telephone reminders are a cost-effective method to diminish PNS, thus increasing access, improving staff and providers efficiency, and decreasing medicolegal risks of patients "lost to the follow-up".

Poster No. 91

Changes in Diet and Parents' Health Perceptions One Year After Pediatric Cholesterol Screening

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The American Academy of Pediatrics (AAP) recommends screening children with a family history of heart disease for elevated serum cholesterol. Little is known, however, about the consequences of labelling children as having hypercholesterolemia. We studied a cohort between the ages of 2 to 15 years who had been screened for elevated serum cholesterol (>175 mg/dl) and whose parents, prior to screening, completed questionnaires about family diet, perceptions of their childrens' health, and attitudes towards high cholesterol levels. Parents of children with elevated cholesterol levels (HI, n = 119) and parents of age-and-sex matched controls with normal levels (NL, n = 119) were resurveyed one year later to evaluate changes in attitude and behavior.

Most parents completed both surveys (72% HI, 87% NL). Families reported eating diets lower in cholesterol and saturated fats post-screening (71% HI vs. 31% NL, p<.001) and said children paid more attention to their diets than before screening (71% HI vs. 31% NL, p<.001). HI parents were more likely to worry about their children's cholesterol than NL parents (77% vs. 25%, p<.001) as were HI children compared to NL children (40% vs 8%, p<.001). Parents did not differ in how much they worried about their children's health. Surprisingly, HI parents were significantly *less* likely than NL parents to think of their children as less healthy than others and to think that high childhood cholesterol leads to adult heart disease or makes children more susceptible to illness.

In spite of worrying about their children's cholesterol levels, HI parents report better diets as well as improved perceptions of their children's health post-screening; NL children and parents worry about cholesterol levels despite normal screening values.

Poster No. 92

Enhancing Otoscopic Skill of Pediatric Residents

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Using videotaped otoendoscopic examinations (VOEs) of tympanic membranes, we developed an educational intervention intended to enhance the otoscopic diagnostic accuracy of pediatric residents. Previously, VOE diagnoses had been established as valid, reliable, and able to distinguish between clinicians with differing levels of diagnostic accuracy. First-year pediatric residents (PL-1s) were tested with VOEs, stratified by accuracy score, and randomly assigned within strata to a "supplemented" (N = 6) or a "usual" (N = 6) teaching group. Each PL-1 evaluated 6 patients in each of 3 or 4 clinic sessions. Supplemented PL-1s were percepted by skilled otoscopists, who also used tympanometry, VOEs, slides, minilectures, and publications in the course of teaching. Usual PL-1s received consultation from the same or other preceptors upon request only.

On initial VOE testing, each group averaged 78% correct responses. After completing the clinic sessions, the supplemented group averaged 88%, and the usual group, 80% (P = .02). At the final session, levels of agreement between PL-1s' and skilled otoscopists' independent diagnoses were 90% (mean kappa .77) for the supplemented group and 80% (mean kappa .58) for the usual group (P = .09). For the study group as a whole, correlation between VOE scores and levels of agreement between PL-1s and skilled otoscopists gave an r value of .85.

These preliminary results were obtained in a limited number of PL-1s and they may have been confounded by the study's location in a teaching hospital in which otitis media care and research are emphasized. The results support further study to determine the effectiveness of intensive teaching of otoscopic diagnosis to trainees of various types in various settings.

Poster No. 93

Pediatric Residents Improve Well Child Examinations During a Six Month Training Experience

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Pediatric residents rarely have an opportunity to critique their own skills or to be observed by faculty. We videotaped second year residents as they provided well-baby care. Each resident was recorded at the beginning and end of a six-month ambulatory rotation. The examinations were standardized as follows: (a) residents had not previously met the parents, (b) infants were 2-10 weeks old, and (c) the medical record was only available to the resident after the encounter. With a clinician and a behavioral scientist, each resident critiqued his/her video on 51 items considered to be important by the American Academy of Pediatrics.

Trained observers, blinded as to the dates of the examinations, later independently rated all tapes. Interobserver agreement on scoring of the tapes ranged from 76 to 98 percent. Over the period of six months, the residents improved their scores an average of 11% (P<0.05).

Video-assisted interactive review is a feasible and reliable method of providing formative evaluation, and when coupled with a 6-month ambulatory rotation, has a significant impact on residents' clinical skills.

Poster No. 94

Physician Interview Style and Maternal Disclosure of the Use of Corporal Punishment

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Corporal punishment has both short and long-term consequences for child mental health. This study examines how spontaneous maternal disclosures of its use are related to pediatricians' interactional style during primary care visits. The study took place at an inner city teaching hospital; 52 second and third year residents took part. Children ages 6 mos-12yrs were eligible if they came with their mother for a scheduled visit with their own doctor. With consent, audiotapes of visits were analyzed to classify doctors' and mothers' utterances and to list topics discussed. Disclosures of the use or threat of corporal punishment were made in 46 of 232 recorded visits (20%). Third year residents elicited more disclosures (in 31% of visits) than late or early second year residents (24% and 9%)(p<.0001). The variation among resident cohorts was not related to child sex or age, reason for visits, total number of problems discussed, or sex of physician. Within cohorts, disclosure correlated with doctors asking more questions about psychosocial issues (r = .34, p<.01) and giving more medical information (r = .49, p<.001), and with parents giving more psychosocial information (r = .38, p<.01). We conclude that open discussion of psychosocial issues promotes disclosure of corporal punishment, but early in training residents elicit fewer disclosures despite having interactional styles similar to older residents.

Poster No. 95

A Comparison of Resident and Faculty Learning Styles and Implications for Teaching

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Since teaching and learning are reciprocal sides of the same process, this study was undertaken in the Pediatric Department of an urban training hospital to characterize resident and faculty learning styles and report to faculty findings which might be useful in improving their teaching. The Kolb Learning Style Inventory (LSI) was administered to 17 residents and 21 faculty. The inventory has four scales - Concrete Experience (CE), Reflective Observation (RO), Abstract Conceptualization (AC) and Active Experimentation (AE) - derived from self-ranking of selected groups of words. Strongest areas were analyzed and groups compared. A chi square test showed a significant difference in distribution of scores between residents and faculty at P = < .01.

	CE	RO	AC	AE
Residents	40.5%	0%	19%	40.5%
Faculty	7%	0%	77%	16%

Faculty were consistent in AC as their strongest area, while residents were more heterogeneous with CE and AE dominant areas. This clear contrast in distributions is different from other studies in medical settings using the same instrument. Because learning styles influence student/teacher interaction, faculty need to consider these findings when designing and delivering instruction to residents.

Poster No. 96

Home Availability of Ipecac: Our Actions Speak Louder Than Our Words

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Despite recommendations that families with young children have ipecac at home, only about 25% comply. Few studies have examined how best to insure ipecac availability in the home. We enrolled 149 families visiting our Continuity Clinic (CC) with children 6 mos-5 yrs old in a prospective trial of direct distribution of ipecac. A test of poison-related knowledge was administered to all families when enrolled; information about poisonings and use of ipecac was then presented. Families were randomized by clinic session to receive either a coded ipecac sample (MED) or a coded prescription (RX) to be filled at our hospital outpatient pharmacy. 3-4 months later families were retested by phone and asked to provide the code number on their ipecac.

115 families (58 MED, 57 RX) were followed-up. Poison knowledge improved in both groups. 74% MED and 60% RX families had ipecac ($p=0.10$). When we excluded 39 families (17 MED, 22 RX) who went to our pharmacy for other prescriptions, there were 32/41 (78%) MED, 18/35 (51%) RX with ipecac at home ($p=0.01$).

Conclusion: Despite equivalent improvements in knowledge, families receiving MED were more likely to have ipecac than those receiving RX. We should give ipecac to families.

Poster No. 97

Pediatric Education in Emergency Medicine Residency Programs: Ten Years Later

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The purpose of this study is to examine the changes in the pediatric education of emergency medicine residents over the last decade. Questionnaires were mailed to the training directors of all emergency medicine residency programs. Sixty-five (79%) of programs responded. While children represented 29±2% of all patients seen in the surveyed institutions, only 17 (26%) programs provide more than 6 months of pediatric education—no increase in the last decade. EM residents frequently rotate through pediatric emergency departments (72%), inpatient pediatrics wards (51%), and intensive care units (88%). Most physicians in charge of pediatric education are EM trained (75% vs 29% in 1981) and only 12% are pediatric emergency medicine fellowship trained. Despite several improvements and the increased satisfaction of program directors, the pediatric component of EM residents' training continues to be disproportionate to the number of children in the emergency medicine patient population. Pediatric emergency medicine specialists should strive to play a more significant role in the pediatric education of EM residents.

Poster No. 98

Maternal Identification of Persistent Suppurative Otitis in Young Children

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Follow-up for suppurative otitis media is often scheduled at 2 weeks if the concern is persistent suppurative otitis, or at 6 weeks if the concern is middle ear effusion. A screening method that could accurately predict which children need to be seen at two weeks could decrease unnecessary visits. This study addressed: 1) What is the risk of persistent suppurative otitis in young children (3-24 months), 2) Can mothers identify that their young child's ear infection has resolved.

Private practitioners in our collaborative ambulatory research group were trained to be valid otoscopists. 379 children between the ages of 3 and 24 months with acute otitis media were then enrolled. All were treated and returned for recheck 10 to 17 days later. Data were obtained about risk factors, current symptoms, mother's opinion of ear status, and clinical ear findings.

Mothers were able to correctly identify resolution (Predictive value 88%, Chi sq., $p=.000$). Mothers were less likely to identify that the child had persistent otitis (42% predictive value), particularly if this was a first child or the child had >3 prior infections. At recheck 24% of otitis had not resolved. Night waking or new cold symptoms (15% of the subjects) were the only risk factors associated with unresolved otitis (46% and 51%, log. regress. $p=.01$, $.04$ respectively).

A mother's judgement that otitis has resolved can be used to replace the 2 week otitis recheck for most children under two. However, if a mother believes otitis is still present an ear recheck is needed to confirm it.

APA TOPIC PLENARY SESSIONS
Wednesday, May 6, 9 AM-NOON

CLINICAL ISSUES

The Utility of the Urinalysis (UA) in Making a Presumptive Diagnosis of Urinary Tract Infection (UTI) in Children

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Purpose: Characterize the utility of certain elements of the UA, singularly or in combination, in identifying children with UTIs (positive urine cultures).

Methods: Laboratory results for urine specimens subjected to both UA and culture (UC) in an on-site outpatient clinic (office) laboratory over a 27-month period were reviewed. All specimens were collected by midstream void technique, urethral catheterization or suprapubic aspiration from children whose physicians requested the urine studies to assist in documenting a possible UTI. Specimen processing was initiated within 10 minutes of collection. UA and UC were by standard techniques. All patients with a positive UC were symptomatic. Sensitivity (SE), specificity (SP) and positive (+PV) and negative (−PV) predictive values were determined for each test or combination of tests. RESULTS: 92 (15.4%) of 598 specimens were positive.

	SE	SP	+PV	−PV
Dip stick: Leukocyte esterase (LE)	80.4	72.7	34.9	95.3
Nitrites (N)	33.7	100.0	100.0	89.2
LE or N (DIP)	83.7	72.7	35.8	96.1
Microscopic: White blood cells (WBC)	76.1	85.6	49.0	95.2
Bacteria	98.7	73.5	37.7	99.7
WBC or BACT	98.7	67.6	33.1	99.7
Dip stick or Microscopic: DIP or WBC	88.0	71.2	35.7	97.0
DIP or BACT	100.0	59.9	30.2	100.0
Any test	100.0	59.5	30.0	100.0

Conclusions: The combination of DIP or BACT had a SE and a −PV of 100%; WBC had no more value than a DIP; N had a SP and a +PV of 100%. An on-site office laboratory can provide UA results that have a highly significant association with UC results.

Preferences for Short Term and Permanent Clinical Outcomes

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Decision analysis aids medical decision making by combining probabilities with patient preferences. While probabilities, by their nature, are quantitative, the quantification of patient preferences remains a fundamental challenge. This challenge is evidenced by the multiple instruments used to measure preferences. However, only one method, the standard gamble (SG), embodies the axioms of decision analysis by incorporating patients' attitudes toward the inherent risks they must face. These attitudes are especially pertinent when patients must balance a high probability of short term adverse outcomes with a low probability of permanent loss.

To examine the importance of risk preference, we assessed the preferences of pediatricians and parents using two methods, the visual analogue scale (VAS) and the SG. Preferences for three short term outcomes (venipuncture, oral antibiotic therapy, and hospitalization) and two permanent outcomes (death and profound neurologic disability) were assessed to determine if the method of assessment affected the decision of choice in a previously published decision analysis involving the care of febrile children.

The VAS and the SG yielded strikingly different results. When we used the VAS, the decision of choice was to avoid blood tests and antibiotic therapy regardless of the risk of bacterial infection. The VAS consistently overestimated the decrement in patient preferences for short term outcomes by a factor of one million to ten million, when compared to the SG. By contrast, using the measurements obtained with the SG, the decision of choice was to treat all patients even when the risk of bacterial infection was minute.

We conclude that incorporating risk attitudes into patient preferences using the SG profoundly affects decision making. When patients' risk attitudes are included, short term outcomes are of trivial importance even when probabilities of permanent detrimental outcomes are miniscule. Decisions made without considering patient's risk preferences may misrepresent their true wishes.

Efficacy of the Young Infant Observation Scale (YIOS) in Correlating Clinical Appearance (CA) With Infectious Outcome in Febrile Young Infants

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We correlated the YIOS score with infectious outcome of 248 febrile infants 0-8 weeks old receiving sepsis evaluation [SE], physical examination [PE], LP, CBC/blood culture, U/A/urine culture]. The 7 variables assessed [level of activity, alertness; respiratory effort; peripheral perfusion; muscle tone; affect; feeding pattern] were graded either 1 [no compromise], 3 [moderate compromise], or 5 [severe compromise], generating a total YIOS score [range 7-35]; based only on grading of variables, infant CA was labelled "well" or "ill". Variability in interobserver grading was N.S. 32 had serious bacterial infections [+SBI: 10 bacterial meningitis, 13 bacteremia, 7 UTI, 2 *Salmonella* GE]; 45 aseptic meningitis [+AM]; and 171 culture-negative with normal CSF [Cx−]. Compared to +AM and Cx−, +SBI had a significantly $>$ [$p<0.01$] mean total YIOS score, rate of total YIOS score >10, and rate of "ill" CA. 3 of 32 +SBI had a total YIOS score of 7 [no compromise], all 3 had an abnormal SE [CSF pleocytosis, WBC count $>15{,}000/\text{mm}^3$, or pyuria/bacteruria]. A combination of total YIOS score of 7, no focus of infection on PE, and normal SE had 99% sensitivity and 98% negative-predictive value for +SBI.

Cow Milk Formula vs Soy-Based Formula After Acute Diarrhea: A Randomized Controlled Trial

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The choice of formula for refeeding of bottle-fed infants with acute diarrhea living in a developed country is controversial. A randomized double-blind controlled trial of infants from 2-12 months of age was conducted to determine whether soy-based formula shortened the duration of diarrhea compared with cow milk formula. Infants who were admitted to our tertiary care Canadian hospital, as well as outpatients seen in the Outpatient Department and offices of pediatricians affiliated with the hospital, were eligible. The duration of diarrhea and proportion of treatment failures, defined as diarrhea >7 days, formula refusal, persistent vomiting and recurrent diarrhea were compared. 39 infants receiving soy-based formula and 34 receiving cow milk formula were similar in age, gender, enrolment weight, and duration and nature of illness before enrolment. The duration of diarrhea was significantly longer (Student's *t* test, $p=0.03$) in those receiving cow milk (mean, 6.6 days) than in those receiving soy-based formula (4.5 days). The difference in weight gain was not statistically significant. Of the thirteen hospitalized patients, a trend ($p=0.14$) towards a longer hospitalization was observed in the cow milk recipients (2.7 days) compared with the soy recipients (1.6 days). There was a higher proportion of treatment failures in cow milk recipients ($p=0.08$). Soy-based formulae significantly shorten the duration of acute diarrhea in infants in develped countries. We recommend that soy-based formulas should be considered as the first choice in infant refeeding after acute diarrhea.

Prospective Evaluation of Complications of Local Anesthesia for Neonatal Circumcision

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Use of the dorsal penile nerve block (DPNB) for anesthesia in neonatal circumcision has been shown to be effective in decreasing pain and stress for the infant. In spite of these data, there has been reluctance to recommend routine use of DPNB, primarily because of concerns about its safety.

A prospective evaluation was undertaken of neonatal circumcisions performed with DPNB. A questionnaire was completed by the medical caregiver at the time of the hospital discharge exam and at the two week well visit for all circumcised infants, noting: type of clamp used; DPNB use; degree of bruising from anesthetic injection; complications of DPNB; complications of circumcision; and any other significant clinical illness.

480 infants were prospectively evaluated. 414 patients (86%) had no complication relating to DPNB or circumcision. The only complication noted from DPNB was bruising at the site of injection in 53 (11%). All bruising had resolved by the two week visit and no baby was felt to have had any clinical symptoms related to the bruising. 19 (4.0%) patients were felt to have a complication related to circumcision.

In this prospective study of infants circumcised using DPNB, bruising was the only complication of the anesthesia and was not felt to be clinically significant. When coupled with the large body of data on its effectiveness in decreasing pain and stress during neonatal circumcision, we feel the data strongly support the routine use of DPNB for neonatal circumcision.

Streptococcal Pharyngitis in Young Children

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One hundred and fifty children from a community pediatric clinic, aged 3 mos to 5 yrs, with signs of pharyngitis, temperature ≥ 38°C and untreated by antibiotics during the preceeding week, were included in this prospective study. Nose and throat cultures were taken from each child. Blood antistreptolysin (ASO) was examined. If the cultures were positive for GAS, a second blood sample for ASO was obtained later. True streptococcal infection was defined in case of a positive culture and an increase in the ASO titer of at least 2 tubes, while positive culture without significant changes in ASO titer were defined as carriers. Positive GAS cultures were found in 24 cases. True GAS infection was found only in patients >2 years old (Fig.) The carriers of GAS increased gradually from 3% during the 1st year to 22% by the 5th year. This study demonstrated that in the population evaluated the incidence of true GAS infection in children <2 yrs of age is low as was observed in the past.

Breast Feeding and Recurrent Otitis Media in the First Year of Life

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Objective: Assess relation of exclusive breastfeeding (EBF) to recurrent otitis media (ROM) in first 12 mos.

Design: 1216 infants enrolled in the Tucson Children's Respiratory Study were followed prospectively.

Variables: Duration and exclusiveness of breast feeding, timing of introduction of formula and supplemental foods; ROM (3 episodes in 6 mos. or 4 episodes in 12 mos.); and other potential risk factors (day care, siblings, sharing a bedroom, gender, smoking, family allergy, education).

Results: 182 (15%) of 1216 infants had ROM. The rate of ROM was 11.9% in infants exclusively breast fed for ≥ 4 mos., 15.7% in those breast fed ≥ 4 mos. but supplemented with foods or formula before 4 mos., and 20.1% in those who were not breast fed or breast fed <4 mos. ($p<0.007$).

Conclusions: Controlling for above variables EBF for the first 4 mos of life has a protective effect against ROM which is independent of the other risk factors considered.

Dimercaptosuccubate (DMSA) as Chelation Agent for Children With Low Level Lead Toxicity: An Open Pilot Trial

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Identification and elimination of lead source(s) are of primary importance for children who have elevated Blood Lead Levels (BLLs). Controversy exists over the methods and benefits of chelation therapy when BLLs are less than 1.9 µmol/L (40 µg/dL). An open trial with DMSA was completed in order to formulate a protocol for its outpatient use and to evaluate its safety and compliance. Results are reported for 17 patients, mean age 22 months, who completed 1 or 2, 19 day courses. All 17 patients had lead base surface paints identified in their homes. A minimum number of chelations occurred while the child remained in a lead paint contaminated home, they are identified as "Source +". "Source −" children had lead abatement completed prior to onset of chelation. Mean BLLs (µmol/L) are presented here:

	#:	PRE:	Range:	POST:>3 weeks
		Results of 22 single chelations		
Total	22	1.60	(1.04-2.95)	1.18 (p<.001)
Source +	6	1.53	(1.09-1.90)	1.40
Source −	16	1.74	(1.04-2.95)	1.07 (p<.001)
		Final Results of 17 patients (#1 or 2 courses)		
Total	17	1.71	(1.04-2.95)	1.00
Source +	4	1.45	(1.09-1.90)	1.33
Source −	13	1.8	(1.04-2.95)	0.87

Three patients developed self limited diarrhea and emesis while 1 developed a rash while on DMSA. CBCs with differential and urine analysis were unaffected by DMSA treatment. DMSA appears safe for outpatient use and is more effective when lead abatement procedures have been completed. Randomized, prospective trials are needed to determine if DMSA augments the lowering of BLLs beyond that accomplished by environmental abatement alone.

Severity of Lower Respiratory Illnesses (LRIs) in Infants: Prediction at Presentation

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Approximately 30% of infants have at least one LRI identified in the first year of life. Hospitalization rates for LRIs in infants vary greatly (1-30%). This study was designed to develop clinical guidelines that identify infants with LRI for whom hospitalization may be safely avoided.

During the winters of 1989-90 and 90-91, data were collected from 195 visits by infants who presented with LRI to the outpatient department of one hospital. A severity score was based on the assumption that risk for apnea or respiratory failure justified hospitalization. Points were assigned for prematurity, age <2 months, sympathomimetic and theophylline drug use, IV fluid use, abnormal blood gas or oxygen saturation, and ventilator use. Risk classification was based on total points. Of all 62 hospitalized subjects, proportions classified as no, slight, moderate, and high risk were 13%, 26%, 30%, and 21%, respectively. All 133 patients not hospitalized fell into the no risk category.

The dependent variable, risk, was dichotomized for analysis: low risk (no or slight risk) and non-low risk (moderate or high risk). In bivariate analyses (X^2) predicting non-low risk, age <3 months, grunting, flaring, worsening overall status (described by the parent), O_2 saturation <90%, pulse (P)≥160, respiratory rate (RR)≥70, state (an index based on arousal, attentiveness, vocalization, movement, color, capillary refill, quality of cry and consolability), and overall severity (assessed by the physician) were statistically significant ($P<.05$). In multivariate (logit) analysis, statistically significant predictors of non-low risk included P≥160 (O.R. = 2.2) and RR≥70 (O.R. = 5.5). P≥160 plus RR≥70 had a sensitivity, specificity and negative predictive value of 74%, 61% and 90% respectively, for non-low risk. Guidelines including only P and RR to select for non-hospitalization would select low risk infants in 90% of cases in our study population.

Management of Febrile Infants (FI) 15 to 28 Days of Age With Intramuscular (IM) Ceftriaxone (CTX) and One Day of Inpatient Observation

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Standard care of FI under 28 days of age usually includes 72 hrs of IV antibiotics pending the results of bacterial cultures. We hypothesized that selected FI 15 to 28 days of age may be managed by one day of hospitalization and IM CTX. We followed 105 FI 15-28 days of age with fever ≥38°C, who were nontoxic, had no source on physical exam, a peripheral WBC $<20\times10^9/L$, CSF WBC <10mu10^6/L, and negative urine WBC esterase. After obtaining blood, CSF, and urine cultures, the FI received 50 mg/kg of IM CTX. FI were then admitted for 24 hrs of observation, received a second dose of CTX and were discharged. FI were followed up by telephone at 2 and 7 days and were recalled to the hospital if cultures grew a bacterial pathogen. 6 FI (5.7%) had serious bacterial infections (SBI) identified. One FI had *E. coli* meningitis, bacteremia, and UTI, 2 had group B streptococcal bacteremia, 2 had UTIs (*E. coli* and *P. mirabilis*) w/o bacteremia, and one had *Salmonella* gastroenteritis. Infants with and without SBI did not differ (p>.05) in age, temperature, WBC, %bands, or absolute band count. 5 of the 6 FI with SBI had their cultures grow a pathogen before they were discharged. All were well during their hospitalization. The FI with *Salmonella* gastroenteritis was discharged to home without diarrhea and recalled to the hospital 3 days later when the stool culture grew *Salmonella*. 1 of 99 patients without an SBI became ill with diarrhea and tachypnea during 12 hrs of hospitalization and required an IV line and oxygen. 4 of 99 patients without an SBI required hospitalization after discharge for either a new fever 2 or 7 days after discharge, a contaminated culture, or inguinal adenitis 9 weeks after discharge. We conclude that 24 hours of hospitalization and IM CTX is a safe alternative to 3 days of IV antibiotics for non-toxic FI 15-28 days old, who after a full evaluation for sepsis do not have a bacterial source identified.

Reevaluation of Criteria to Identify Infants Evaluated for Possible Sepsis (PS) at Low Risk (LR) for Serious Bacterial Infection (SBI)

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Infants ≤60 days evaluated for PS who are previously healthy (full term and without a history of phototherapy for hyperbilirubinemia, underlying illness, or prior antibiotic therapy), appear well, have no focal infection, a WBC count 5-15,000/mm^3, a band count <1500/mm^3, spun UA <10 WBC/HPF and stool smear <5 WBC/HPF (if diarrhea) are considered at LR for SBI. To verify these LR criteria, 979 infants evaluated for PS in the emergency department or clinic at one of the collaborating centers were prospectively studied from 7/84-6/91. 885 appeared well and had complete data available to assess risk status and 461 (52.1%) met the LR criteria. 4 (0.9%) LR infants had SBI: 2 had bacteremia and 2 had UTI. The negative predictive value (NPV) of the LR criteria for SBI is 99.1% (95% CI = 97.6-99.7%). The sensitivity of the LR criteria is 93.9% (95% CI = 84.4-98.0%). The NPV of the LR criteria for bacteremia is 99.6% (95% CI = 98.3-99.9%). These data confirm the clinical utility of the current LR criteria.

To determine if exclusions from the LR group could be decreased, items used to define previously healthy and focal infection were analyzed. No infant excluded from the LR group only by a history of prior antibiotic therapy (N = 38) or otitis media alone (N = 26) had SBI. Including such infants in the LR group simplifies the clinical application of the LR criteria and improves the NPV.

Septic Arthritis (SAH) Versus Transient Synovitis (TSH) of the Hip: The Value of Screening Labs

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This study was undertaken to determine the true diagnostic value of the initial erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and temperature (T) in differentiating SAH from TSH. Patients were selected from a retrospective chart review if they met the following criteria: limp, pain, or refusal to bear weight in whom the physical exam localized the pathology to the hip; decreased range of motion of the hip; single joint involvement; no trauma; no radiographic bony abnormalities; no distant invasive bacterial infection or evidence of rheumatologic disease. Charts were reviewed by one author blinded to the ESR, WBC, T, diagnosis and treatment to determine the study diagnosis of TSH (N = 94) or SAH (N = 38) or other (not in study).

RESULTS	SAH	TSH	RELATIVE RISK	95% CI	P.
ESR>20 mm/hr	79%	28%	4.96	2.46-9.96	.0000003
ESR>30 mm/hr	71%	14%	5.52	3.05-10.0	.0000000
T>37.5 C	66%	30%	2.77	1.57-4.90	.0004
T>38.0 C	45%	15%	2.62	1.60-4.28	.0006
WBC>15,000/mm^3	26%	16%	1.50	0.84-2.67	NS
ESR>20 or T>37.5	97%	47%	22.48	3-19-158.6	.0000003

Conclusions: 1) There is clinically significant overlap in the ESR, WBC, and T; and 2) all children with an irritable hip without a clearly identified source who have an ESR ≥ 20mm/hr or TEMP >37.5° C should be considered for diagnostic hip aspiration.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Maternal Rating of Child Health at School Age for VLBW Children: Persistence of the Vulnerable Child Syndrome

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Experience of severe or life-threatening illness in infancy may lead to maternal perceptions of increased vulnerability of the child to illness irrespective of subsequent health persisting well into the preschool period. The influence of past and current child health and environmental factors on maternal perceptions remains poorly delineated. In this prospective multi-center study using the Rand General Health Index, we found that mothers continue to rate both the current and past health of very low birth weight (VLBW, ≤1500g) (n = 610) children as poorer than heavier birth weight children (n = 1252) up to

8-10 years of age. Other significant univariate predictors for lower rating of child health included current child health status (specific conditions, functional limitations due to health problems, and mental health), past health (prolonged neonatal and subsequent hospital stays) and environmental factors (indicators of socio-economic disadvantage, poor maternal mental health). In multivariate analyses, measures of past and present child health continue to be highly significantly associated with maternal perceptions of health with the exception of behavior problems, where variables related to pregnancy variables (mode of delivery, birth order, plurality), socio-economic status and maternal health (including mental health) were no longer associated with maternal ratings. However, VLBW continued to exert a highly significant effect. The multivariate model was highly significant (p<0.0001) and accounted for 40% of the variance in maternal report. We conclude that 1.) maternal ratings of child health are related to past and present child health status and are not affected by environmental factors; and 2.) that VLBW continues to influence maternal perceptions of health even at school age independent of past and current health.

Beneficial Behavioral Effects of Successful Encopresis Therapy

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There has never been an adequate demonstration of the beneficial effect on emotional maladjustment of successful treatment of encopresis, nor that laxative therapy (incl. enemas) is free of emotional adverse effects. We studied the impact of standard paediatric treatment in 162 children over a minimum 1 year follow-up (from a RCT of multimodal therapy versus behavior modification alone), and compared baseline data to 88 children from a fracture clinic. The measures used were the Child Behavior Checklist (CBCL), Teacher Report Form (TRF), and the Hyperactivity Scale of the Conner's Questionnaire (HC). Maladjustment rates were: CBCL, 60 (36%), compared to 6% of controls (p<.001); TRF, 37 (31%), compared to 1 (1.3%) control (p<.001); HC, 49 (30%) encopresis subjects scored in the clinical range. There were large and highly significant improvements in CBCL and HC associated with remission.

	Encopresis same				Improved				Remission			
Gains	Nx	x	(se)	p	N	x	(se)	p	N	x	(se)	p
CBTL	23	0.4	(1.91)	.85	43	2.2	(1.38)	.11	84	3.0	(0.99)	.003
TRF	15	-1.2	(2.16)	.47	28	2.6	(1.56)	.10	39	1.0	(1.33)	.57
HC	23	0.7	(1.14)	.54	43	1.4	(0.82)	.09	82	2.8	(0.59)	.001

25 children (15%) were referred for psychiatric assessment and management, in whom there was a large and significant deterioration in CBCL Sum-T (adjusted gain −4.01 (SE 1.99), p = .046). Examination of CBCL Profiles did not show evidence for appearance of new behavior problems in successfully treated children. The gains on the CBCL Sum-T scores were 3.6 (SD 10.51) for the multimodal therapy group, and 2.7 (SD 8.19) for the behavior modification only group, but the between group contrast was not significant (p = .71). We conclude that successful medical therapy for encopresis results in improvement in behavior disorder in children, and that the treatment does not cause new emotional problems.

Pediatricians' Approaches to Developmental Problems: 15 Years Later

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Whether recent advances in developmental pediatrics have influenced pediatric practice is uncertain. We interviewed, in their offices, 41 randomly selected, board-certified, primary care pediatricians in Connecticut to explore their attitudes and clinical approaches to developmental problems. Responses were compared to those from an identical study of 97 New England pediatricians performed 15 years ago.

Important changes in certain clinical approaches and attitudes were found. Pediatricians are less likely to rely on history and physical examination alone to confirm a suspicion of mental retardation (p<.001) and are more likely to refer such a child to a psychologist (p<.001); they are more likely to perform hearing screening in evaluating a child with delayed speech (p<.044); they are more likely to contact the school in evaluating a child with school failure (p<.001) and are more likely to refer such a child for further assessment (p<.001). Pediatricians are currently more likely to rate their developmental training as adequate (p<.021).

Results indicate favorable changes in pediatricians' approaches to developmental problems and support the greater emphasis on developmental issues in pediatric education.

The Usefulness of the Battelle Developmental Inventory Screening Test

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The BDIST is designed to detect developmental problems in children 6 months to 8 years of age. In several states, it is a preferred measure for child-find efforts because it: (a) has separate subtests for each of seven developmental domains; (b) produces a range of scores which conform to varying state eligibility criteria; and (c) has national standardization. Nevertheless, there is little data on the BDIST's accuracy. The present study was undertaken using 104 children between 7 and 83 months of age who attended one of five day care centers. One psychological examiner administered diagnostic tests of intelligence, achievement, speech-language and adaptive behavior, while a second, blind to diagnostic testing, administered the BDIST. The BDIST was found to be highly sensitive—detecting, at the 1.5 cutoff, 80% of the 20 children diagnosed with developmental problems. Since 74% of the 84 non-handicapped children passed, the BDIST had moderate levels of specificity, except that children 4 years and older tended to be over-referred. Although continued development of the test is needed, the results suggest that the BDIST approaches standards for developmental screening tests. Further, the receptive language subtest was found to be as sensitive as the total BDIST although somewhat less specific. Because it takes only five minutes to give, the receptive language subtest appears useful for routine prescreening in health care settings.

Family Factors Influence Psychosocial Diagnoses

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Studies of pediatricians' diagnoses of psychosocial problems (PSP) have ignored family influences. We examined the impact of family factors on pediatricians' diagnoses of PSP in a random sample of 19 practices in New Haven, CT. Families of all 4-8 year-old children were recruited during 2 3-week periods (Fall, 1987; Spring, 1988). Of 2006 eligible families, 1886 (94%) participated. Families who indicated that the enrolled child had a problem on the Child Behavior Checklist or families with children pediatricians identified with a PSP (N = 919) were invited to be interviewed, as well as a randomly chosen 1/2 of families whose children had no PSP. Of those invited (1383), 1148 participated (83%).

These families were 77% white and 56% had mothers with >12 years of education. When asked if they *would* seek a pediatrician's advice for any of 6 PSP (e.g., learning, behavior), 80% said they *would*. Looking at those families who reported that their children *actually* had one of the PSP (677), only 42% *had* discussed the problem with the pediatrician. The 677 families were identical to the entire population on sociodemographic and health-related variables. If families reported that they had discussed PSP, pediatricians were 1.3 times more likely to diagnose children with a problem compared to children whose families did not discuss PSP (60% vs. 46%; $x^2 = 13.0$; p = .000). This relationship held after adjusting for pediatricians' training in PSP, type of visit, and how well physician knew the child.

We conclude that too little attention has been paid to family influences in the pediatricians' diagnostic progress. Pediatricians must educate families about the PSP they can address and encourage families to share PSP.

Pediatric Clinical Assessment of Mother Child Interaction: Concurrent and Predictive Validity

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While pediatric clinicians routinely assess mother-child interactions (MCI) during health supervision visits, the association of these assessments to concurrent MCI measured in other settings, and their worth in predicting future MCI and child status has not been previously evaluated. The observation component of the PROCESS (Pediatric Review of Children's Environmental Support and Stimulation), which assesses MCI in a standardized format during health visits, was collected on 46 consecutive infants (63% black, 50% male) by one pediatrician at 8 months gestation corrected age (GCA) during a prospective study of low birth weight, pre-term infants. A large range of child variables and the HOME Inventory were collected at 12 and 36 months GCA. Pediatric Clinical Rating (PCR) of MCI correlated with the 12 month HOME total score (r=.62, p<.000) and the 36 month total HOME (r=.67, p<.000). The PCR did not correlate with 12 month Bayley MDI (r=.08), but was strongly associated with 36 month Stanford Binet (r=.54, p<.000), Child Behavior Checklist (r=−.36, p=.02), and mutuality (r=.46, p=.001) and maternal supportive presence (r=.46, p=.002) in a 30 month parent child laboratory session. When PCR was entered with infant birth weight and maternal education as predictor variables into separate regression equations against the above 36 month dependent variables, the PCR independently contributed (p≤.04) to each outcome. Low scores on the PCR identified a group with lower average 12 month HOME (27.6 vs 35.9, p<.000), 36 month HOME (26.1 vs 40.5, p=.0001), the 36 month child Stanford Binet (81 vs 97.3, p=.002), the mutuality (2.1 vs 2.9, p=.01) and maternal supportive presence (3.1 vs 4.1, p=.02) in the 30 month parent child session, and higher scores on the Child Behavior Checklist (58.1 vs 42.9, p=.02).

The pediatric assessment of MCI in health supervision visits is associated with other concurrent and future measures of mother child interaction, and offers clinical information important to the prediction of child development and behavioral outcomes.

Communicating Medical Bad News: Parent Preferences and Experiences

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Limited information about appropriate ways for physicians to communicate bad news to parents stimulated this study of physician communication. 189 parents of children enrolled in 15 developmental daycare centers received questionnaires that examined the experience of being told bad news and elicited preferences for physician behavior in a hypothetical situation using both closed and open-ended queries. A majority of parents experienced their physician displaying a high degree of control of the conversation (65.3%) and a high degree of confidence (58.1%). Most parents were allowed to talk a great deal (55.0%) and found the physician highly caring (51.3%). Many were given little information (42.0%) and mental retardation was not discussed to any great extent (40.4%). Some physicians displayed little of their feelings (35.5%) and some gave parents little opportunity to show feelings (31.0%). Compared to their experiences, parents preferred significantly (P<0.001) more communication of information and feelings. Their strongest preferences were for physicians to show caring (96.5%), to allow parents to talk (95.3%), and to be allowed to show their own feelings (93.5%). They want the physician to share information (90.0%) and to be highly confident (88.(%). Most parents (87.1%) strongly desired parent-to-parent referral but only some (18.6%) were ever referred.

There is a large difference between what parents experience and what they desire in physicians who communicate bad news. While physicians were found to control the interaction and be highly confident, parents especially value physicians who show caring and allow them to talk and share their own feelings.

Resident Response to Psychosocial Issues

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Although a major goal of the child health supervision visit is detecting and providing guidance about psychosocial issues, a number of recent studies have found that psychosocial concerns are not consistently addressed. We had previously documented that physicians responded to only 40% of psychosocial concerns of school-aged children.

The purpose of this study was to determine how effectively psychosocial issues are addressed in infants <2 years. Thirty Five videotapes of visits to 13 pediatric residents by children aged 2 weeks to 2 years were reviewed using a coding system with established psychometric properties. A total of 77 psychosocial concerns were raised during these visits. The psychosocial concerns included: 35% sleep practices, 33% parenting practices, 14% child care issues, 10% family relationships, 8% child behaviors. Resident physician responses to these concerns were as follows: 9% of the concerns were ignored, 22% were acknowledged, but no information or reassurance was provided, 12% reassurance was provided to the parent, and 57% specific information or action was given. Specific information and action was provided more frequently than for school age children where the response distribution for the above categories was 17% ignore, 43% no information, 3% reassurance, 37% information/action (χ^2, 3 d.f., =8.0, p<.05).

Pediatric residents performed somewhat better in effectively addressing psychosocial concerns in younger children. Since children are seen much more frequently during this age group, residents have many more opportunities to practice dealing with the different psychosocial issues raised in this time period. This study also reveals that residents specifically elicit and provide opportunities to discuss psychosocial issues and address these problems in the younger age group. However, further educational efforts are indicated to improve resident performance in discussing psychosocial issues in both younger and older age groups.

Mother-Child Interaction and the Development of Infants With Disabilities

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Prior studies have demonstrated that mother-child interaction is sensitive to clinical intervention and predictive of later child behaviors. We hypothesized that improved maternal interactive skills would be associated with developmental gains in infants with disabilities.

Interaction was assessed for 190 mothers and their disabled infants (M=10.6 mos.) at entry to early intervention (T1) and 12 months later (T2). Although mean maternal interaction scores showed modest change, a subgroup (12%, n=23) increased > 1 standard deviation. This subgroup did not differ demographically or in child function from the rest of the sample at T1, but differed on the full set of child outcomes at T2 (MANOVA F=3.82, p=.005). Univariate tests indicated greater gains in adaptive behavior (F=4.52, p=.035), spontaneous play (F=5.73, p=.018), and child interactive skills (F=10.3, p=.002), but not in cognition.

These findings underscore the potential impact of positive change in maternal interactive skills on the development of a range of functional behaviors in infants with disabilities.

Screening Mothers of Young Children for Substance Abuse

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We wished to develop a brief, sensitive screening questionnaire to detect maternal substance abuse. The screening questions were compared with the 25-item Michigan Alcoholism Screening Test (MAST) and the 20-item Drug Abuse Screening Test (DAST) on a self-administered survey conducted at five pediatric clinics (2 university clinics, 2 private, and 1 military). The MAST or DAST were completed by 507/752 mothers of children under 6 years of age; most subjects were Caucasian (78%) and married (75%). Overall, 18% were positive on the MAST and 3% were positive on the DAST. Rates were highest in the University clinics, intermediate in the military clinic, and lowest in private practices (17%, 11% vs 4%, respectively, P<0.001). The four screening questions about alcohol (including binge drinking and tolerance) and the two questions about drug use had a completion rate of over 80%. A positive response to one or more of 4 questions about drinking had a sensitivity of 93% compared with the MAST. The MAST detected only 25% of those who reported physiologic tolerance to alcohol and only 32% of those who were binge drinkers. The question "Have you ever had a drug problem?" had a sensitivity of 88% compared to the DAST; the DAST failed to detect any of those who reported using drugs in the day prior to their clinic visit. Pediatricians who wish to screen for maternal substance abuse can use 4 questions about drinking and 2 questions about drug use which have high rates of completion, good sensitivity compared with longer instruments, and detect more drinking problems and drug use than are uncovered with the MAST/DAST.

Clinical Preventive Service Efficacy and Adolescents' Risky Behaviors

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Most adolescent mortality and morbidity is attributable to risky behaviors. Office based clinical preventive services to identify and modify risky behaviors have been proposed, however, such programs have often been challenged because their efficacy has not been demonstrated.

To examine the value of studying or implementing office based clinical preventive services for adolescents, we developed a cost-effectiveness model for youths' risky behaviors. The model considers two strategies: standard practice versus a screening and intervention program which involves annual screening visits for all adolescents and three additional counselling visits for youth identified as high-risk. We considered two risky behaviors (drunk driving and unsafe sexual activity) and five outcomes (motor vehicle crashes, motor vehicle deaths, unintended pregnancy, HIV infection, and other STD's). Current prevalence estimates and direct cost estimates were used to calculate the baseline cost-effectiveness of the program and the minimum efficacy at which the program would be cost-effective. Using this threshold efficacy, we determined sample sizes required for a trial of the program.

Assuming that the program is 5% effective at preventing risky behaviors, it would cost $22,000 to prevent any one adverse outcome, and $1,550,000 to prevent a death from a crash or from HIV. Assuming society were willing to pay $600,000 to prevent a death (a generally accepted figure), the program would be cost effective only if it were 8.2% effective at changing behavior. Unfortunately, measuring changes in outcomes at this efficacy would require a clinical trial with between 5300 and 1.4 million adolescents in each treatment group.

Studying clinical preventive services to prevent adolescents' risky behaviors would be impractical. The decision to implement these programs should be made based on current knowledge and beliefs; their efficacy can probably only be studied as part of widespread implementation.

Correlates of Mental Health of Caregivers of Severely Ill Children

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Indicators of mothers' mental health are associated with psychological status and function of their children with chronic illness. We studied depressive symptoms (DS) of caregivers of severely ill children and the association of DS with selected family characteristics.

562 parents with children ages 0-16 years with severe illness responded to surveys. Children had spina bifida, BPD, developmental delay (DD), AIDS, or other conditions requiring technology assistance (TA). DS were measured by the Center for Epidemiologic Studies-Depression Scale. Parents reported income, family structure, social support (SS), child functional status, and impact of illness on family (IOF).

50% of the caregivers had DS scores above the cutoff for clinical depression. High DS scores were associated with high IOF scores (total score and financial subscale) and with lower household income ($p<0.01$); caregivers in single-adult households were 39% more likely to be above the cutoff than those with other adults ($p<0.01$). Caregivers of children with AIDS or with *both* DD and TA had higher DS ($p<0.05$), but otherwise diagnosis and functional status were not associated with DS.

Health professionals caring for children with special health needs should be aware of a high risk of depression among parents, especially when single or financially stressed.

EMERGENCY MEDICINE AND CHILD ABUSE

Contact Burn Injuries Among Children in an Urban Emergency Department

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Previous studies have reported that scald burns are the most frequent cause of burns in hospitalized children. To determine the profile of burn injury among an ambulatory population, we conducted a retrospective chart review of all first visits by patients under age 18 receiving care in the Emergency Department of Hartford Hospital for a burn injury incurred between October 1, 1988 and September 30, 1989. Of the 110 visits, contact burns accounted for 43.6%, followed by scalds (34.5%), flame and explosion (10.9%), cigarette (5.5%), electrical (2.7%), miscellaneous (1.8%) and unknown (1.0%). For children under the age of 11, contact burns caused over 50% of all burns. The mean age of children with contact burns was 3.6 years compared to 6.3 years for all others ($p<0.02$). Irons accounted for 43.8% of contact burns and 19.1% of *all* burns in this study, making it the single most frequent agent by which children were burned. Next most frequent were beverages (13.6%), cooking-related (10.9%), tap water/baths (6.4%), foods (6.4%), cigarettes (5.5%), and fireworks (5.5%). In this study 14 children (12.7%) were admitted as inpatients. Only 3 of 48 (6.3%) children with contact burns were admitted, compared with 7 of 38 (18.4%) with scalds ($p<0.03$). Child protection referrals were less common for children with contact burns (3; 6.3%) compared to those with scald burns (5; 13.2%) but this difference did not reach statistical significance. We conclude that although apparently less severe than scalds, contact burns are a more common cause of morbidity in our urban population. Strategies for prevention of contact burns, specifically those caused by irons, should be further investigated.

Vaginal Discharge as a Marker of Gonorrhea in Pre-Pubertal Females

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The presence of a sexually transmitted infection in the young child who is alleging sexual abuse is a powerful adjunct to the diagnosis and ultimate protection of the child. Policy at Children's Hospital Medical Center (CHMC) is to culture all children who allege sexual abuse for genital, rectal and pharyngeal N. gonorrhea, and genital and rectal C. trachomatis. The cost of obtaining these cultures is high and can be stressful to the child. If children who are at high risk for an STD could be identified the number of STD cultures would be kept to a minimum.

We retrospectively reviewed the charts of 622 pre-pubertal females (age <12 yrs) who were seen at CHMC for evaluation of alleged sexual abuse between January, 1989 and August, 1991 or were diagnosed with an STD. The items that we reviewed included, Tanner stage, chief complaint, history of abuse or genital contact, exam findings, finding of genital trauma and the presence of vaginal discharge.

During the study period, 28 children were found to have STDs. 22 (3.5%) of these children had vaginal GC. All 22 had a vaginal discharge. There was a history of sexual abuse in 2 of these girls at the time of the initial evaluation. In 9 girls, the history of sexual abuse was not illicited until after the diagnosis of vaginal GC had been made. The incidence of vaginal chlamydia infection was 1.3% (8/622). Of the six girls with vaginal chlamydia without GC, only one had a vaginal discharge.

It is well known that asymptomatic infections are common in the adolescent population, but there are conflicting reports about the presentation of STDs in the pre-pubertal age group. Our review suggests that in the pre-pubertal female, vaginal gonorrhea is always symptomatic. In addition, our findings suggest that all pre-pubertal girls with a vaginal discharge should be cultured for gonorrhea. We have begun a prospective study at CHMC looking at STDs in the pre-pubertal age group in an effort to gain more insight into this issue.

Reproducibility of Field Prognostic Indicators in Pediatric Submersion Victims Receiving Prehospital Care

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Study Objective: To test previously determined prognostic outcome indicators in pediatric submersion victims who received prehospital care.

Study design: Restrospective cohort study

Setting: Non-icy waters of King County, Washington

Measurements: We studied all submersion victims <20 y/o who were treated by Seattle and King County Emergency Medical Services (EMS) between 1985-1989 and were hospitalized or died following the submersion incident. We identified victims from EMS incident logs, hospitals' discharge and medical examiner's registries. The presence of previously determined outcome predictors were correlated with the victim's outcome at hospital discharge. *Results*: We identified 77 submersion victims. Of twenty-nine victims in cardiac arrest, 13 had return of spontaneous circulation following field resuscitation. Of these, 6 (21%) survived, two with mild neurologic impairment at hospital discharge. The best outcome preditors were obtained in the field. These were, for death or severe neurologic impairment, submersion intervals >10 minutes (6/6), resuscitation intervals >25 minutes (17/17), and for good outcome, sinus rhythms (37/37), reactive pupils (43/43), and neurologic responsiveness (40/40) at the scene. Hypothermia was not predictive and did not protect victims with prolonged submersions.

Conclusion: Field determined prognostic factors were reproducibly good outcome predictors. Our data support pronouncing dead in the field pediatric victims of non-icy submersions who do not respond to advanced cardiac life support within 25 minutes. Aggressive EMS may save the lives of pediatric victims with short submersion times in cardiac arrest.

The Impact of Criminal Courts on Sexually Abused Children

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Many professionals are concerned about the potential for harm to sexual abuse victims from societal intervention. Our work suggested that civil (juvenile) court involvement might speed healing in children. We undertook a prospective cohort study of children involved in criminal court to assess whether adjudication and testimony in that setting has a similar impact on the subsequent mental health of these victims.

All children ages 4 to 18 years and their caretakers referred to prosecutors offices in 4 large cities over a 22 month period, were approached; 35% (289) agreed to participate. Data about the abuse, family, and perpetrator were collected from records. Several measures, including the Child Assessment Schedule, assessed the child's functioning at referral, and again nine months later. A history of court/treatment experiences was obtained at follow up. An intervention stressors inventory, with weighted scores for prototypic experiences, allowed us to estimate the intrusiveness of intervention for each child. Intervention scores for the children were compared to changes in the levels of anxiety, depression, somatic complaints and sexualization, behavior problems, and overall distress.

Follow up data were collected on 256 children (89%). The sample was 83% female and 68.5% white with a mean age of 9.9 years. For 53% the perpetrator was a family member; for 5% the perpetrator was a stranger. Penetration occurred to 65% and force was used on 36%. The children had a 17.4% reduction self reported distress nine months later. Frequency and harshness of testimony were associated with less resolution of depression (P<.01). Maternal support was related to better psychological functioning at both Time 1 and Time 2.

Understanding Fatal Child Abuse

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Prevention of fatal child abuse requires an accurate current description of the problem. Medical, social service and coroner reports were reviewed for 12 cases of fatal child abuse identified at a children's hospital from 1988-1991 (2.0% of all referrals for suspected physical abuse).

The median age was six months (range 24 days to 3 years). Two patients previously had suspicious injuries. Five families (41.7%) had prior protective service involvement; however, four cases involved not the patient but a sibling.

All patients presented in critical condition and had retinal hemorrhages. Seven had skull or rib fractures; two were nonacute. The cause of death in all patients was blunt impact head injury; one also had intraabdominal injuries. Postmortem findings showed soft tissue head injury in 100%. Specific findings included acute subdural hematoma (8), subarachnoid hemorrhage (6), cerebral edema (6), subacute subdural hematoma (3); and cervical spine injury (1).

Nine cases were ruled due to homicide; eight have come to legal closure resulting in five felony convictions. These findings confirm previous studies and emphasize the role of blunt impact brain injury. Of particular importance for prevention are (a) the paucity of prior injuries, and (b) among families known to child protection agencies the focus was usually not the fatally injured child. These findings have significant implications for prevention efforts.

Exposure to Violence Among Inner City Parents and Young Children

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While the prevalence and impact of violence against mothers and children has been studied, similar issues regarding observing violence has not been. To determine the prevalence and correlates of exposure (observation or victimization) to violence, we consecutively recruited 116 parents (86% of those eligible) with children 1-5 y.o. from the Pediatric Clinic at Boston City Hospital. Mothers were English speaking, minority (81% black, 14% Hispanic), and poor (63% living on < $10,000/yr). In response to a standardized questionnaire, 31% of mothers reported seeing a knifing or shooting and another 47% had seen someone shoved, kicked or punched. Twenty percent of events occurred in the last month, 68% in the last year; 33% reported seeing more than one assault. 18% of mothers were victims of a knifing or shooting, and another 26% had been shoved, kicked or punched. According to mothers, 7% of children had seen a knifing or shooting, 45% had seen someone shoved, kicked, or punched. No children were reported to be victims of violence.

Comparisons among mothers who were victims of violence (V), observed violence (O), and those who were neither (N) revealed that mothers exposed (O and V) to violence felt less safe (57% V vs 42% O vs 20% N, p<0.03), and worried more about getting shot or killed (49% V vs 72% O vs 33% N, p<0.02) compared to nonexposed parents. Parents whose child had observed violence limited their movements (80% O vs 57% N, p<0.01) and worried that their child would be beaten up (69% O vs 45% N, p<0.02.). Based on maternal self-report, an important number of mothers and young children observe violence which may have an impact on maternal caretaking and the wellbeing of both mother and child.

Adolescents Trying To Conceive: An Association With Child Sexual Abuse?

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Victims of childhood sexual abuse are at increased risk for adolescent pregnancy. This may be the result of earlier, more frequent, less well-protected sexual activity or from having a greater desire to conceive compared to their never-abused peers. To distinguish between these two possibilities, we studied the reproductive and sexual histories of 200 sexually active 13-18 year old females in relation to self-reported sexual abuse.

Anonymous questionnaires revealed that 40 (20%) of the 200 subjects had been abused. T-Test and chi-square analyses revealed no differences between abused teens and their non-abused peers in the mean age of first intercourse (14.37 years, SD 1.37), the frequency of sexual intercourse, or the consistency of birth control use. Abused teens, however, were more likely to: state that they were trying to conceive (35% vs 14% p<0.01), report pressure from boyfriends to conceive (76% vs 44% p<0.01), report fears about their ability to conceive (38% vs 16% p<0.01), and to report discussing these fears with others (60% vs 32% p<0.01).

Our study suggests that childhood sexual abuse may increase the risk of adolescent pregnancy by fostering the desire for pregnancy in adolescence. Further study is needed to determine whether this desire reflects a fear of infertility, the desire to please their boyfriends, or other factors. The efficacy of adolescent pregnancy prevention programs may be improved by identifying previously abused adolescents and by designing educational interventions which specifically address their desire to conceive.

An Emergency Department Trial of Continuously vs. Intermittently Nebulized Albuterol

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It is suggested that continuously nebulized albuterol (CA) may be effective in the initial therapy of acute asthma exacerbations. Seventy-two 6- to 18-year-old children with asthma (FEV1 less than 60% predicted) were assigned by day of treatment to receive either CA at a dose of 0.5 mg/kg/hr (max 15 mg/hr) for the first hour, or intermittently nebulized albuterol (IA) at a dose of 0.15 mg/kg (max 5 mg). Spirometry was performed before the first treatment and 30, 60 and 90 minutes later. IA patients were treated at an average interval of 63 minutes. Mean % predicted (%pred) FEV1 in IA patients increased from a baseline of 33.3% ± 13.3 to 48.4% ± 20.2 at 30 minutes and remained constant thereafter. For CA patients (%pred) FEV1 increased from a baseline of 35.6% ± 12.8 to 50.8% ± 19.9 and also remained constant. Side effects were mild and similar in both groups. Continuous administration of albuterol during the first hour of therapy is both effective and safe, but results in improvement in FEV1 and in a side-effect profile not significantly different than standard intermittent nebulization given at approximately hourly intervals.

The Successful Use of a Metal Detector in Locating Coins Ingested by Children

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Recent studies indicate that despite current recommendations, most asymptomatic children do not undergo radiologic evaluation following a coin ingestion. The purpose of this study was to examine the accuracy of a metal detector in locating coins swallowed by children. All pediatric patients presenting to the Emergency Department at Loyola University Medical Center following a coin ingestion were eligible for participation in the study. Following an interview and physical examination all patients were scanned with a Super Scanner (Garrett Security Systems, Inc. Texas) metal detector and underwent chest and abdomen radiography. Sixteen children, ranging in ages between 9 months and 6 years (mean age of 3 years), participated in the study. The metal detector correctly identified the presence or absence of coins in fifteen (94%) patients, as confirmed by radiographic studies. Both examinations were negative in three patients and swallowed coins were correctly located in twelve patients. The metal detector failed to locate a coin in the rectum of a patients who presented 26 house after ingestion. We conclude that the metal detector evaluated by us is highly accurate in locating swallowed coins.

Utility of Routine Laboratory Testing in the Pediatric Trauma Patient

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We assessed the prevalence of laboratory abnormalities and the sensitivity and specificity of the physical examination [PE] and screening laboratory tests (CBC, electrolytes, BUN, creatinine, glucose, SGOT, SGPT, amylase, lipase, U/A) for identifying intraabdominal injury [AI] in moderately injured pediatric patients. The records of 288 consecutive Level II trauma patients were reviewed. All patients were received directly from the scene and had the following data recorded: mechanism of injury, Glasgow coma score, trauma score, pediatric trauma score, systematically recorded PE findings, laboratory results and injuries detected during hospitalization. SGOT and SGPT were obtained in 59% of patients, glucose was obtained in 78% of patients; each of the remaining tests was obtained in $>85\%$ of patients. The overall prevalence of laboratory abnormalities was 5.5%.

Fourteen patients (4.8%) were identified with a total of 17 significant AIs (5 splenic, 5 renal, 4 hepatic, 3 pancreatic). The PE combined with U/A showing >20 RBCs/hpf had a sensitivity of 100%, specificity of 66%, positive predictive value of 13%, and negative predictive value of 100% for the detection of patients with AI. The presence of laboratory abnormalities suggesting injury did not increase the sensitivity of the model and significantly decreased both specificity and positive predictive value. When this model was applied to 91 additional trauma patients identified by ICD-9 codes as having AI, the PE and U/A identified an abnormality in 89 (97.8%) cases [95% C.I. = 94.8% - 100%]. We conclude that in the moderately injured pediatric trauma patient: 1) there is a low prevalence of laboratory abnormalities; 2) the PE combined with U/A is highly sensitive in detecting AI; and 3) laboratory testing seldom identifies unsuspected injury.

Violence in the Pediatric Emergency Department (PED)

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Directors of PEDs with fellowship programs were surveyed to identify the frequency of violence and the perception of safety in pediatric EDs. Over half of the 77% (30/39) responding reported ≥ 1 verbal threat per week, 77% reported ≥ 1 physical attack on staff per year, and 23% reported actual injury to staff. No PEDs had weapon detectors or city police stationed there, and half had 24 hour security.

The majority report their staff practice with at least occasional fear (57%) and have documented this concern (87%). Perception of safety was influenced by the incidence of verbal threats ($p < .02$), injury to staff ($p < .04$), and the frequency security is needed ($p < .001$). PEDs with $\geq 60{,}000$ visits per year were more likely to have multiple physical attacks on staff [RR 3.7 (95% CI:1.6-8.6); $p < .01$]. Physical attacks and verbal threats increase with longer waiting times ($p < .05$). Only 22% of PEDs with reported injuries had 24 hour security compared to 60% of those without injuries ($p < .05$). PEDs are not immune to the problem of violence. Efforts need to be directed to increase safety through better security, more efficient patient care, and aggression management training.

Access to Care for Children Visiting the Emergency Room (ER) With Acute Exacerbations of Asthma

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To determine differences in access to continuing and preventive care among pediatric patients utilizing an urban ER for treatment of acute exacerbation of asthma, we prospectively surveyed families of 170 patients (ages 2-18 yrs, mean age 7.4 yrs). The interview schedule instrument generated information about socioeconomic factors, source of medical care, medication use, and plans for management of asthma including the family's plan for accessing a source of continuous care during an acute exacerbation.

Of 170 patients, 81 (52%) had Medicaid, 71 (45%) private insurance, and 5 (3%) were self paying. A primary physician (MD) or clinic could be identified by 162 patients (95%). Seventy seven (46%) called their MD or clinic before reporting to the ER. "Come to the ER" was part of the management plan for 56 patients (33%) and was the only plan for 34 (20%). Regular preventive therapy (cromolyn, theophylline, or steroids) was used by 45 patients (27%). Allergy evaluations had been previously performed for 59 patients (35%).

Patients with Medicaid, compared to those with private insurance, were less likely to call their MD or clinic before coming to the ER ($p = .0001$), more likely to have "come to the ER" as part of their asthma management plan ($p = .0002$), and less likely to have had an allergy evaluation ($p = .028$). Patients with previous allergy evaluation were more likely to be on regular preventive therapy ($p = .0001$), more likely to have called their MD ($p = .003$), and more likely to have a plan other than "come to ER" ($p = .047$). Patients with Medicaid had a greater number of prior hospitalizations for asthma ($p = .007$) compared to those with insurance.

The majority of patients in this study could identify a source of primary care. However, patients on Medicaid were significantly less likely to access continuing and preventive care and more likely to utilize the ER. Efforts stressing education and improvement of access to continuing care may benefit this underserved population.

GENERAL PEDIATRICS

An Analysis of Group versus Individual Health Supervision Visits

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Objective: This study compared the effectiveness of group health supervision (three or four infant/parent units counseled as a group for one hour) to traditional individual visits in conveying knowledge of child care and development, increasing perceived maternal support, and mitigating maternal depression.

Method: Subjects were first born infants and their mothers recruited from a suburban pediatric practice. They were over 95% white, predominantly middle-class, and married. Of the 50 families who completed the study, 25 were sequentially allocated (in subgroups of 3 or 4) into group health supervision (GHS) and 25 to individual visits (controls). All visits were conducted by the same person (RLR) at 2, 4, 6 and 10 months. A questionnaire covering knowledge of child care and development (CDQ), the Maternal Social Support Index (MSSI), and the Center for Epidemiologic Studies Depression Scale (CESD) were administered to both groups before their 2 month and after their 10 month visits.

Results: The mean difference between pre- and post-test scores for the intervention (GHS) and control groups were compared using the Student, t-test as follows:

TEST	GHS	(SEM)	CONTROLS	(SEM)	p-value
CDQ	5.08	(0.75)	3.24	(0.68)	.07
MSSI	0.28	(0.79)	0.48	(1.11)	.88
CESD	2.00	(1.33)	4.38	(2.11)	.35

Twenty four % (6/25) of mothers in GHS were depressed (CESD scores >15) on pre-test and 4% (1/25) on the post-test as compared to 40% (10/25) and 16% (4/25) respectively for controls.

Conclusion: These findings suggest that mothers in GHS acquire more knowledge of child care and development and tend to be less depressed as compared to those who have traditional visits.

Children Without Health Insurance: Prior Coverage and Expectations for Future Coverage

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Objective: To assess prior health insurance coverage and parental expectations for future coverage among families with an uninsured child.

Design: Telephone interview of a parent. *Setting:* Monroe County, New York.

Subjects: 144 uninsured children enrolled at the Strong Memorial Hospital Pediatric Continuity Clinic, Emergency Department, or the County Health Department Immunization Clinic.

Results: 79% of children had been previously insured. Prior coverage included commercial or union plans (33%), Blue Cross/Blue Shield (29%), HMO (18%), and Medicaid (3.5%). Loss of coverage was due to: loss of employment (41%), ineligibility for Medicaid (23%), lack of an affordable premium (7%), and dissatisfaction with coverage (5%). 56% of parents had inquired about obtaining health insurance for their child. 55% felt that their child might be Medicaid eligible, but only 1.6% had inquired about Medicaid. 84% had never received any help in obtaining insurance coverage for their child. 86% stated that being informed about affordable health insurance would be very helpful. Most parents felt able to pay monthly premiums for health insurance (13% didn't) ranging from up to $10 (19%), $10 to $30 (35%), to more than $30 (23%) per child. 81% felt able to contribute a copayment of up to $5 (41%), between $6 and $15 (33%), to more than $15 (8%) per child for a medical visit. Parents felt the following services should absolutely be covered by insurance: hospitalization (86%), emergency department visits (84%), surgical procedures (85.4%), well-child visits (75%), sick visits (78%) and medications (57%).

Conclusion: Health insurance coverage is not static; most uninsured children were previously insured. Parents expressed an ability to contribute amounts for health insurance that are small relative to the extent of coverage desired.

A Successful Randomized Control Trial to Increase the Use of Cloth Diapers

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There is a debate concerning the adverse environmental effects of both cloth and disposable diapers. The purpose of this randomized clinical trial was to evaluate: 1) an office based, educational intervention to promote the use of cloth diapers and 2) how parental diapering choices are influenced by the use of cloth diapers in the nursery in which their child in born. In the office intervention, advice/written material on the advantages/disadvantages of cloth diapers were given to parents at the two week visit. In the hospital intervention cloth diapers were used exclusively by the nursery. 193 subjects were enrolled and divided into four groups receiving: (1) neither intervention (N = 66); (2) the educational intervention only (N = 77); (3) the hospital intervention only (N = 27); and (4) both interventions (N = 29). All groups were similar with respect to choice of diapers in previous children, education, insurance status, and presence of siblings. Use of cloth diapers was measured by direct observation at the first three child visits. At six weeks the use of cloth diapers was 24% vs 37% vs 44% vs 48% in groups 1, 2, 3, 4. As compared to group 1, the subjects in group 2 (educational intervention only) and group 3 (hospital intervention only) were 1.8 times (95% CI = 0.9-3.6 and 2.5 times (95% CI = 1.0-6.3) more likely to use cloth diapers. Those in group 4 (educational and hospital intervention) were 2.9 times more likely to use cloth diapers as compared to group 1 (95% CI = 1.2-7.2). At three and six months the results were similar. We conclude that counseling by pediatricians can enhance the use of cloth diapers, but that a change in hospital policy is a more powerful influence. The combination of these two interventions leads to an even greater change in parental behavior (increase use of cloth diapers) than either alone.

Career Choices and Satisfaction: A Comparison Between Practitioners and Academicians

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A 1984-85 random sampling of 2000 Fellows of the AAP was conducted to compare those factors that influence the career choice and satisfaction of pediatric practitioners and academicians. Instruments included the Job Descriptive Index, Stress Scales, Rezler's Learning Preference Inventory (LPI), and the FIRO-B Scale. Nine hundred fourteen Fellows responded to the survey. Academicians reported being more satisfied with their careers ($P < .0001$), felt certain they had made the right career choice ($p < .004$), and were more stressed than practitioners ($p < .01$). They were more likely to "express control" ($p < .001$) on the FIRO-B, but had a stronger preference for abstract ($p < .0001$), student-structured ($p < .0001$), and interpersonal learning ($p < .001$) on the LPI. Practitioners had higher scores on "want control" ($p < .037$) on the FIRO-B, and stronger preferences for concrete ($p < .0001$) and teacher-structured learning ($p < .0001$) on the LPI. These differences have implications for continuing education and the career counseling process.

Improving Access to Services for the Poor

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Although programs exist which entitle poor families to assistance for their unmet needs, large numbers of families do not have access to them. MD's routinely have access to poor children yet do not understand entitlement programs. The Medicolegal Services Project, a joint program between Harvard Medical and Law Schools is an attempt to address these problems. A structured 30 minute interview is used to determine family income, housing conditions, out of pocket medical expenses, work status. The questionnaire is designed to focus on solvable service and income support needs of patients rather than to identify all of their social and economic problems. Uninsured and medicaid patients with scheduled appointments are asked to participate while waiting for their MD appointment. At the end of the interview a computer program generates the names of programs for which a family qualifies. To date 25 families have been interviewed, 23 families had access problems. The most common problems encountered were AFDC, WIC and SSI. Using advice and advocacy the team resolved 44% of access problems encountered within 3 months. Most were resolved with minimal intervention. Primary physicians were unaware of 94% of all problems encountered. We conclude that MD's can *systematically* assess and redress concrete issues of social need in their offices. They may also wish to ally themselves with local legal aid societies. We plan on making the program available to other interested parties when it is complete.

Clinical Characteristics of Children Proposed to Receive Tympanostomy Tubes

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Placement of tympanostomy tubes for recurrent or persistent middle ear disease is the most common reason for children to undergo general anesthesia. We took advantage of a unique national database to examine the clinical characteristics of children under 16 years old proposed for tympanostomy tubes. Data were collected prospectively by telephone by trained nurses as a part of a national system for quality assurance currently used by firms which insure over 10 million people in the United States. We reviewed 3970 cases from 49 states scheduled for tympanostomy between January, 1990 and September, 1991.

The median age at time of proposed surgery was 1.7 years (mean 2.9). Sixty percent were male. Persistent middle ear effusion was given as the reason for surgery in 30%, recurrent acute otitis media in 20% and both in 47%. The average duration of effusion was 147 days (range 2 days to 5 years) and 69% of children with effusion had hearing loss of 20 dB. Effusions were treated with an average of 4.3 courses of antibiotics. Drugs used most commonly included cefaclor (56% of patients), amoxicillin (49%), trimethoprim-sulfamethoxazole (37%), amoxicillin-clavulinate (35%), erythromycin-sulfisoxazole (18%) and cefixime (17%). Children with recurrent otitis averaged 5.0 acute episodes in the six months prior to review (range 0 to 18) and 76% received antibiotic prophylaxis, for a mean of 33 days. One quarter received prophylaxis for less than two weeks.

These data offer a detailed clinical look at a national sample of children proposed by otolaryngologists for tympanostomy tubes. The data show a good deal of diversity and could be useful to pediatricians in comparing their practice to national norms and to reseachers in designing studies to extend our knowledge about the effectiveness of tympanostomy tubes.

Prevalence of Viral Pathogens on Fomites in Day Care Facilities

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Transmission of infectious diseases in child day care centers is facilitated by microbial contamination of environmental surfaces. The specific sites of contamination within the day care environment have not been completely defined. We conducted a 12 month study in order to identify high risk environmental sources of contamination in 2 day care centers. *Methods.* The polymerase chain reaction was utilized to detect the presence of viral pathogens. Viral nucleic acids were extracted from environmental samples, amplified by reaction with oligonucleotide primers and detected by hybridization and polyacrylamide gel electrophoresis. Bacterial pathogens were detected and characterized by means of standard microbiological methodologies. *Results.* Initial analysis indicate that rotavirus RNA can be detected in water playtables (3′ × 6′ × 6″ table filled with water) as well as telephone receivers and other environmental samples. Water playtables were also found to be contaminated with a range of potentially pathogenic bacteria including, Klebsiella oxytocia, Pseudomonas aeruginosa, and E. Coli as well as species of Flavobacterium. *Conclusions.* Liquid surfaces used for play may serve as major sources of contamination within the day care environment. The identification of contaminated surfaces and subsequent disinfection may reduce the transmission of infections in the day care environment.

What is the Cost of Health Care for Foster Children?

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Chronic illness among foster children may place a heavy financial burden on an already stressed foster care system. The purpose of this study was to determine the health conditions and associated health care expenditures of foster children in Washington State. We compared the health care expenditures of foster children to those of non-foster children. All foster children ages 0-7 years ($n=1772$) continually eligible for Medicaid during 1990 were identified using Washington State Medicaid program eligibility files. Expenditures for these children were compared to a systematically sampled cohort of non-foster children ($n=5316$) in the Aid for Families with Dependent Children (AFDC) program. A computerized file of Medicaid claims was analyzed to determine total expenditures, associated medical conditions, and procedures. The average per capita health care expenditure was \$3,245 for foster and \$549 for AFDC children ($P<.001$). Health care provider, medical equipment and inpatient hospital costs accounted for the difference in expenditures. Seven percent of foster children, compared to 0.4% of AFDC children, had medical care costs exceeding \$10,000 per year. This small cohort of foster children ($n=117$), 44% of whom suffered from mental disorders and 33% from congenital conditions, accounted for greater than 65% of all foster children health care expenditures. We conclude that a small group of chronically ill foster children contributes significantly to the total cost of foster care health expenses.

Self-Medication in Childhood: Experience at Summer Camp

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Little is known about self-medication in childhood, especially when children are away from parental influence. A previous pilot study documented that a substantial number of children (31%) were intending to bring medication to a residential summer camp equipped with a well staffed (24 hour coverage) and stocked infirmary. The following summer, at camp entry, a cohort of 414 campers (55% female, ages 9-17) were given a screening interview regarding medication use and attitudes toward self-medication. At the end of camp, eight weeks later, a self administered questionnaire was given to the campers who brought medications. Medicines for specified chronic conditions such as diabetes, thyroid disease, or acne were excluded from this analysis.

One hundred and eighty two children (44%) brought at least one medication to camp (average of 1.5 medications/camper). Eighty-seven percent of medications brought were over-the-counter decongestants, analgesics, and antihistamines, and 13% were prescription antihistamines and decongestants. There were no gender differences observed between those who brought medications and those who did not. An age difference was evident; 50% of children ≥ 13 years old brought medication compared to 35% of children <13 years old ($p<0.01$). The majority of children who brought medications reported that they took them (131/182, 72%). Ninety-two percent of children who reported taking medication, as well as 66% of those who brought but did not take medication, stated that they felt comfortable taking any medication without adult advice. Younger children were just as likely as older children to take medications at camp without informing an authority figure (24% vs 34%; $p=\text{NS}$). Twenty-one percent of those taking medications reported sharing them with friends.

These data suggest that away from parental influence, a substantial number of children, even young ones, self medicate, and share their medications with friends. Awareness of the practice of self medicating among young children should provide an impetus for pediatric providers to educate their patients and families about medication use when performing pre-camp and other physical examinations.

Factors Affecting Pediatricians' Participation in Medicaid in North Carolina

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Although the Medicaid program is expanding, pediatricians' participation in Medicaid is not. We studied the relative importance of factors that influence pediatricians' participation in Medicaid in NC. We surveyed all non-academic primary care pediatricians in patient care at least 50% of their time. We assessed their knowledge of Medicaid reimbursement, attitudes toward Medicaid patients and the Medicaid program, and beliefs about the effects of accepting Medicaid on their practice. Pediatricians who were less likely to accept new Medicaid than non-Medicaid patients were classified as "restricting" access to their practice.

Of the 389 eligible pediatricians, 332 (86%) responded; 29% restricted access. The proportion of pediatricians who restricted access was 62% in cities, 13% in medium-sized towns and 12% in small towns. Among pediatricians in cities, the proportion restricting access varied from 87% to 22%, even though they received about the same percentage of their usual fees for the 2 most common services. Overall, a lower ratio of Medicaid reimbursement to usual fees, pediatricians' attitudes towards the economics of accepting Medicaid, their perceptions of the availability of other physicians and whether they were too busy to care for Medicaid patients were independently associated with restricting access.

The large variation in pediatricians' willingness to provide care for Medicaid patients is not explained by reimbursement. Existing resources for the care of Medicaid patients, pediatricians' economic dependence on Medicaid and local norms of practice may play larger roles in pediatricians' decision to participate in Medicaid. Strategies to improve participation should enlist the support of community physicians, as well as increase reimbursement.

Understanding of AIDS by Elementary School Children: A Developmental Survey

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The aim of this project is to measure the level of understanding about AIDS by elementary school children. Using a new, developmentally-based, semi-structured interview (ASK -- AIDS Survey for Kids), 361 children (57% Black, 24% Hispanic, 19% White; 52% Female) attending kindergarten through sixth grade at four public schools in New Haven were interviewed. Three main concepts (causality, treatment, prevention) were scored for each of three illnesses (colds, cancer, AIDS) based on the conceptual sophistication of the response. Grade level (or age) was the single variable most strongly correlated with concept score for each illness, with a medium to large effect (Pearsonian $R = 0.32 - 0.51$; $p \leq 0.0001$ for each correlation). Verbal intelligence (Peabody Picture Vocabulary Test-Revised) was the only other variable that contributed significantly to the variance observed in concept score in a linear regression model; gender, race, and socio-economic status did not contribute significantly. There was a consistent increasing progression in the percent of children with high concept scores as grade level increased ($p \leq 0.0002$ for each concept by the Jonckheere test of ordinal trend). Children's level of understanding was significantly less sophisticated for the cause of AIDS than for the cause of colds ($p \leq 0.0001$), but not significantly different from that of cancer ($p = 0.7$).

We conclude: 1) concepts about AIDS follow the predicted developmental sequence, little influenced by race, gender, or socio-economic status; 2) the ASK may be a useful new research instrument for studying children's understanding of critical health concepts related to AIDS. These results have direct applications to the creation of developmentally appropriate AIDS education curricula for primary and elementary grades.

The Pediatrician's Private Office as an Ambulatory Placement in a Clerkship Rotation: Physicians' Opinions of the Learning Experience

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With the development of an ambulatory component to the University of Toronto pediatric clerkship, 35 selected university-affiliated pediatricians agreed to accept 82 clinical clerks (33.5% of the 1990 graduating class) in their private offices for a 2 week rotation, without remuneration. Selection of participating pediatricians was based on previous positive student ratings of their clinical teaching. Their opinions regarding the feasibility and value of this experience were elicited by questionnaire (response rate=82.8%).

All preceptors regarded the office placement as a valuable learning experience for students. 97% enjoyed their preceptorship, and 87% felt that it stimulated an academic approach to practice. 96% reported that student contact was favorably accepted by their patients. Although 76% felt significantly slowed down and 41% reported seeing fewer patients per day, all respondents were willing to participate in future rotations.

Most pediatricians (>80%) reported being readily able to assess the students' clinical skills and knowledge and provide critical feedback

(92% reported observing their students conducting patient interviews and physical examinations). Students were considered to have exposure to a broad spectrum of pediatric problems, particularly common illnesses, well-baby and well-child care.

Our data shows that an office-based ambulatory rotation for clinical clerks is feasible, is likely to be supported by pediatric faculty and can provide a relevant experience for students.

PREVENTION AND EPIDEMIOLOGY

Prevalence of Lead Exposure in a Clinic Utilizing 1991 Center for Disease Control (CDC) Recommendations

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The October 1991 CDC recommendations for preventing lead poisoning in young children included lowering the acceptable blood lead level to 0.483 umol/L (10 ug/dL) and utilizing blood lead levels as the primary screen. In anticipation of this change, we screened all children <2 years presenting at well child visits with venipuncture blood lead (VBL). The VBL results of 225 children evaluated 1/1/91-11/30/91 are shown below:

(μmol/L)	<0.483	0.483-0.723	0.724-0.964	0.965-1.205	>1.205
(μg/dL)	(<10)	(10-14)	(15-19)	(20-24)	(>25)
<1yr	58 (73.4%)	14 (17.7%)	4 (5.1%)	2 (2.5%)	1 (1.3%)
1-2 yr	92 (63.0%)	29 (19.8%)	20 (13.7%)	2 (1.4%)	3 (2.1%)

These data demonstrate the high prevalence of lead poisoning based on the new CDC recommendations; lead poisoning in our patient population is found in 21/79 (26.6%) children <1 year and in 54/146 (37.0%) children 1-2 years. Greater efforts at primary prevention are needed for children <1 year. Repeated screening is necessary to identify those who would benefit from increased surveillance and intervention.

Influence of Circumcision Status on Urinary Tract Infections in Pediatric Males

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Uncircumcised infants have been reported to have a 10-20 fold increased risk of urinary tract infections (UTI). However, there is little data on UTI and circumcision status in older pediatric male patients.

A retrospective chart review was undertaken of all male members of a staff-model HMO under 16 years of age with UTI during a 40 month period from 1987-90 to determine the influence of the circumcision status on 1) the age-specific incidences of UTI in this outpatient population. 2) the predominant infecting organism, and 3) the incidence of UTI in boys with a radiographically normal urinary tract.

Seventy-nine males (.067%) with a confirmed UTI (pure growth of >10,000 colonies/cc) were identified. The incidence decreased from .026% in the first year to .07% in the toddler years, and to .04% in adolescence.

In contrast to the circumcised boys, the uncircumcised males had a UTI incidence 2.9 times higher (p <.005), were younger (mean 50 vs. 96 months), and were predominantly infected with E, coli (77% vs. 40%). The incidence of UTI in the boys with radiographically normal urinary tracts was 5.4 times as high (p <.005) in the uncircumcised population compared with the circumcised patients.

These data suggest that relative to circumcised males, uncircumcised boys have an increased risk of developing UTI even after the first year of life.

Injury Prevention Training and Knowledge Among Urban Poor

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Urban poor are lacking in injury prevention knowledge and are at high risk for injury. To study injury prevention knowledge among urban poor using our emergency department we administered a questionnaire covering fire safety, bicycle safety, and poisonings to 135/137 available parents (all <133% of the Federal poverty level). We asked whether they: had a smoke detector in the home; tested the smoke detector; had a bicycle helmet for the child; knew when to use ipecac; had ipecac in the home. We also collected: demographics (child age, ethnicity, parent age, education level, marital status, health insurance), source of health care, and Hx of injury prevention training.

107/135 (79%) owned a smoke detector, 89/107 (83%) tested it; 12/81 (15%) bicycle owners had a helmet; 21/135 (16%) knew when to use ipecac, and 6/135 (4%) had ipecac in the home. 115/135 (85%) had ongoing health care; 35/135 (28%) had injury prevention training. After controlling for demographics and source of health care in a logistic regression model, owning and/or testing a smoke detector, having a bicycle helmet, and knowledge of ipecac were significantly associated with prior injury prevention training (see Table).

	Has Smoke Detector	Tests Detector	Has Bike Helmet	Knowledge of Ipecac
Adj. Odds Ratio	5.8	5.5	5.7	4.2
95% CI	1.2, 28.4	1.1, 26.8	1.3, 24.0	1.4, 12.4

Demographics and source of health care were not consistently associated with injury prevention knowledge.

Parents using emergency services are lacking in injury prevention training and knowledge, even when they identify a source of regular health care. Those who receive training are more likely to practice injury prevention. We propose that inner city emergency departments serve as additional sites to provide injury prevention training to at-risk populations.

Universal Urine Toxicologic Screening in an Urban Nursery

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All newborns admitted directly to a regular newborn nursery from 6/3/91 to 11/1/91 were screened for urinary toxic substances to determine the incremental case identifications over an established policy of targeted screening. Bagged urine samples were collected within 48 hours of delivery and sent to the hospital toxicology laboratory for analysis. Medical records of 1,081 consecutive admissions have been reviewed. No results were recorded for 137 infants (less than 24 hour stay, 22; transferred to intensive care nursery within 6 hours of admission, 14; contaminated specimen, 4; parents refused, 1; specimen not obtained, 94). Of the remainder, 885 infants had negative screens and 59 (5.5% of all admissions, 6.25% of screened infants) had screens positive for drugs not administered by the obstetric service (cocaine, 52; opiates, 2; phencyclidine, 2; barbiturates, 3; amphetamines, 1; ethanol, 2; 3 screens were positive for two drugs of abuse). Using the guidelines for the previously utilized targeted screening, 254 screens would have been ordered and 57 of the 59 infants with positive screens would have been identified. In summary, 5.5% of the infants admitted to our regular newborn nursery were found to have positive urine toxicologic screens. A policy of universal drug screening identified 2 infants who would have been missed by targeted screening, but resulted in an additional 827 tests. We conclude that universal drug screening adds only a small incremental yield (0.24%) over a targeted approach in the study population.

Profile of Uninsured Children in the United States: Lessons From the 1988 National Health Interview Survey-Child Health Supplement (1988 NHIS-CHS)

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School of Medicine and Dentistry

The 1988 NHIS-CHS contains interview data on 17,110 children 0-17 years old, 2,219 of whom were uninsured during the preceding year. Demographic characteristics, health status, source of and access to medical care were compared for uninsured and insured children. 13% of children in the U.S. were uninsured. Age, sex, and family size were similar among the uninsured and insured. The majority of uninsured (71%) lived in the south and west, equally distributed among urban and rural areas. Hispanic and Native American children were twice as likely to be uninsured (p<0.001). The median family income for uninsured children was $18,500. Children living below the poverty level and with a less educated parent were 2.4 and 2.7 times more likely, respectively, to be uninsured (p<0.001). Uninsured children were not healthier than insured children based on reported health status and medical conditions; however, they were 1.5 times less likely to be up-to-date with the AAP guidelines for routine care and were 1.85 times less likely to have seen a physician within the previous year (p<o.001). 80% of uninsured children had a usual source of routine care. However, children without a usual source of routine care were 2.8 times more likely to be uninsured. 65% of uninsured

children received routine care in a private office and 28% in health centers or hospital clinics. Uninsured children were 3.7 times more likely to have no identified source for sick care ($p<0.001$), however they were not more likely than insured children to receive sick care in an emergency department. These data highlight that uninsured children live in families both above and below the poverty level, that they are not healthier than insured children, and that being uninsured is strongly associated with a lack of access to health care.

Maternal Smoking Patterns and Risk of SIDS

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The association between maternal cigarette smoking during pregnancy and an infant's risk of SIDS has been widely reported. This study compared the SIDS risks of infants exposed to maternal smoke both during pregnancy and infancy or only during infancy, to the SIDS risk of infants not exposed to maternal tobacco smoke.

Normal-birthweight infants from the 1988 National Maternal and Infant Health Survey, a nationally representative sample of 10,000 births and 6,000 infant deaths, were examined. Death from SIDS was determined by ICD code on the death certificate of infants who died. 23% of all normal-birthweight infants were exposed to smoke both during pregnancy and infancy. 7% were exposed only during infancy. The SIDS rates for infants in those exposure groups were 219 deaths/100,000 births and 140 deaths/100,000 births, respectively. The SIDS rate among infants whose mothers did not smoke was 63 deaths/100,000 births. After adjustment for demographic risk factors, the odds ratio for SIDS among normal-birthweight infants was 3.0 in the during pregnancy and infancy exposure group and 1.9 in the during infancy only group. These data indicate that both intra-uterine and passive tobacco exposure are associated with an increased risk of SIDS, and are further inducement to encourage smoking cessation among pregnant women and families with children.

Pediatric Injury Mortality and Morbidity: Canadian and American Experience 1965-1987

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Injuries are a major cause of death among children aged 0-14 and account for one in eight hospital separations in this age group. Historical trends in mortality rates and of hospitalization in the two countries may reflect different underlying social, political and health care phenomena. We examined Canadian and American mortality and hospital separation data from vital statistics sources for children aged 0-14. Rates per one hundred thousand and 95% confidence intervals (CI) were calculated. Between 1965 and 1987, age-standardized injury mortality rates fell from 359 (CI 345-374) to 148 (CI 138-158) in Canada and from 279 (CI 275-283) to 180 (CI 177-183) in the United States. The average annual rate of decline, determined by regression, was 11.29 deaths in Canada and 6.03 deaths in the United States. The difference in slopes was significant at $P<.05$. Hospital separation data, available for the period 1970-1987, indicate a higher rate of injury-related hospitalization in Canada than in the United States. In 1970, injury related separation rates were 9,500 (CI 9,454-9,618) in the United States and 12,326 (CI 12,241-12,412) in Canada. By 1987, these rates had fallen to 6,870 (CI 6,848-6,893) and 9,536 (CI 9,449-9,499) in the United States and Canada respectively. This difference was significant at $P<.05$. Possible explanations for these differences in temporal trends, absolute rates and mortality/hospital separation ratio's include, but are not limited to, differences in morbidity rates, few barriers to hospitalization in Canada and differing urban-rural ratio's. These are discussed, together with implications for research and prevention programs.

Television Viewing, Obesity and Physical Activity Among Adolescent Females: Cross-Sectional and Longitudinal Analyses

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A single published study demonstrating a significant association between television viewing and obesity in children and adolescents has received widespread attention. It has been suggested that television viewing displaces participation in physical activity. We examined the relationships between after school television viewing, body mass index (BMI) adjusted for level of sexual maturity and reported levels of physical activity in a school-based, longitudinal cohort of adolescent females ($N=931$, mean age $=12.4\pm0.7$ years at baseline). In cross-sectional analyses, reported daily after school television viewing was not significantly associated with BMI (Spearman $r=.05$, $P=.17$) and only weakly negatively associated with level of physical activity (Spearman $r=-.09$, $P=.05$), accounting for less than one percent of the variance. Slopes of change of BMI and physical activity were calculated from all available data at 7, 14 and 24 months after baseline ($N=301$). After school television use at baseline was not significantly associated with longitudinal change in either variable. Results of cross-sectional and longitudinal analyses were not substantially changed when controlled for the effects of age, race, parent education and parent fatness. Our results, from a large sample of adolescent females, demonstrate no clinically significant relationships between television viewing and BMI, level of physical activity or change in either over time.

Stressful Life Events and Pediatric Medical Visits

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Despite numerous investigations, the relationship of stress to illness is inadequately understood in children. We examined demographic and stress factors that influenced pediatric medical visits in families recruited from 19 pediatric practices in New Haven, CT. Of 2006 families with children aged 4-8 visiting study practices, 1886 (94%) participated. Interviews with parents gathered sociodemographic and stress information, while information about visits in the 12 months after the interview was abstracted from children's medical records. The sample of children was 80% white, 50% male, and 59% were visiting for acute care. Children averaged 1.9 life events per year, and families had an average of 5.1 events. When compared to Blacks, Whites averaged twice the number of acute (4.0 vs. 2.2) and total (6.1 vs. 3.5) visits.

Families who experienced both child and parent stressful events had more acute visits in the following year when compared to families who had only family or child events or neither ($x=14.78$, $p<.01$). When we adjusted for the presence of a medical condition, the relationship between stress and number of illness visits held for children who had no health problems ($x=14.23$, $p<.02$). However, for those children who had a medical problem, stressful events were not related to the use of medical care.

We conclude that families experiencing both parental and child stressful events frequently use acute pediatric services for children with no predisposing medical conditions.

Helmets! All the Pros Wear Them

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Head injuries are the leading cause of death in bicycling accidents. Bicycle helmet use can reduce the incidence of serious head injury by 85%. However, fewer than 5% of school age children utilize bicycle helmets. We evaluated the effect of a helmet promotion campaign in a large metropolitan area which included a specific education and helmet distribution program in a local school(A). Intervention included active participation by the school board, professional sports teams, medical community, TV and press. Press conferences, community education programs, helmet discount coupons, and poster distribution features the initial campaign effort. Helmets were also distributed in school(A) after 4 weeks of safety instruction. Another elementary school(B) acted as a control group. Both schools received the same community intervention.

Interviews of 500 adults in the metropolitan area 1 year after initiation of the campaign revealed: (1) a 23% awareness of the promotion, and (2) that it affected helmet purchase in 16(14%) of 117 respondents aware of the campaign. Factors associated with wearing a helmet included higher SES, male sex, and younger age group (<9 yrs). Helmet use in school A 6 months after helmet distribution was 73% compared to 33% in school B ($p<.0001$). This multi-faceted approach to affect helmet use demonstrated variable success within our community.

Breastfeeding Promotion in Public Health Clinics

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University of Texas Health Science Center, San Antonio

As part of a comprehensive community project to promote breastfeeding, a prospective randomized controlled trial was conducted to assess the effectiveness of an educational intervention to change feeding behaviors in a public health prenatal clinic population (90% Hispanic). Low-income pregnant women ($n=423$) were randomized to three groups. The experimental group received a live peer-modelling session targeting psychosocial barriers to breastfeeding as well as a culturally-sensitive video designed to increase knowledge about initiation of breastfeeding. A partial treatment group received only the video. A control group saw a neutral video about general nutrition. Demographic data at entry (including feeding intent) and feeding outcomes at delivery and 4-6 weeks postpartum were collected by personal interview. Using logistic regression, a significant group effect was demon-strated for primigravidas in both the partial (OR of 3.93; CI = 1.05-14.7) and experimental (OR = 5.16; CI = 1.09-24.4) groups versus controls. No group effect was demonstrated for multigravidas. The study results emphasize the need for evaluation of public programs for breastfeeding promotion and the importance of defining target audiences likely to benefit.

1992 APA International Health Research Award Winner

Risk Factors Associated with Malnutrition in Children Under Five (5) in the Mazowe District of Zimbabwe

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Objective. To determine the risk factors associated with malnutrition in children, specifically those related to the mothers' lack of education, lack of access to land and lack of political and economic power.

Design. Prospective case-control study.

Setting. Community-based outreach clinics in Mazowe District of Zimbabwe from October to December 1990.

Participants. 246 children, aged 6 months to 5 years, from commercial farms ($N=140$) and communal lands ($N=106$).

Method. Malnourished children (cases) were enrolled if their weight for age was <80% of the 50th centile ($N=123$). A questionnaire was administered on nutritional, economic and social factors. For each malnourished child, a well-nourished control (>90% weight for age) of the same sex and age (±3 months) and from the same background was found ($N=123$).

Analysis. Data were analysed using Epi-info version 5.00 and Chi-square or Fisher's Exact Test to compare the 4 groups.

Results. Age distribution (half were under 2 years of age), severity of malnutrition (3%) severely malnourished; 50% stunted), and breast-feeding practises (90% still breast-fed at age two) were similar between commercial farms and communal lands and between cases and controls.

On the commercial farms, significant risk factors for malnutrition were inadequate land for cash crops ($p<0.03$), no gardens to grow vegetables ($p<0.04$), and lack of income-generating projects ($p<0.03$).

In the communal lands, significant risk factors for malnutrition were lack of maternal education ($p<0.03$), having more than 3 children ($p<0.02$), maternal employment ($p<0.0003$), and absence of financial support from the father ($p<0.03$).

Factors which were not important in the pathogenesis of malnutrition were weaning practises, recent infection, maternal knowledge of health care, and maternal knowledge of health care, and maternal decision-making ability. *Conclusion.* This study emphasizes the importance of maternal factors in childhood malnutrition, specifically the availability of land and financial support as well as a limiting of family size and adequate education.

GENERAL PLENARY SESSION

Thursday, May 7, 8 AM-12:30 PM

Correcting Respiratory Rate (RR) for the Presence of Fever

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This study defines what degree of RR elevation can be attributed to fever using a double blind randomized pre and post acetaminophen comparison of vital signs of febrile children presenting to an outpatient clinic. Inclusion criteria were age between six weeks and 24 months, fever between 38.5 and 40.1°C, no serious illness, and no recent receipt of antipyretics or antibiotics. RRs over 1 minute and rectal temperatures were recorded by a trained observer before, and 1 and 1.5 hours (hr) after receipt of 10-15 mg/kg/dose of either acetaminophen (A) or placebo (P). Randomization produced groups A ($n=53$), and P ($n=45$) with similar mean age (12.2 vs 12.8 mos), baseline temperature (39.2 vs 39.1°C), baseline RR (45{S.D.12} vs 44{S.D.11}), and hours of fever prior to visit (42 vs 37 hr). The most common diagnoses were otitis media(49%), viral syndrome(18%), upper respiratory infection (16%) or gastroenteritis (7%). Two children were excluded from analysis due to lower respiratory disease. The mean temperature decrement of group A was 0.4°C at 1 hr and 0.9°C at 1.5 hr compared to slight increases in fever of 0.29°C at 1 hr and 0.26°C at 1.5 hr in group P. Significant decreases in RR occurred in group A compared to group P at 1 hr (7.4 vs 2.7, $p<0.05$) and 1.5 hr (12.7 vs 3.7, $p<0.005$). Individual RR and temperature changes were strongly correlated (Pearson's $r = 0.395$, $n= 97$, $p<0.000$ at 1 hr, and $r= 0.626$, $n=44$, $p<.0000$ at 1.5 hr). By subtracting RR changes of group P from the RR changes of the group A, one can derive an RR correction factor of 6.8 (1 hr) to 7.7 (1.5 hr) for each one degree °C reduction achieved using an antipyretic.

Intergenerational Patterns of Child Abuse: Do Girls Who Were Abused Grow up to Maltreat their Children?

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and Yale-New Haven (Conn) Hospital

We conducted a cohort study to determine whether children of women who themselves were physically abused during childhood are at an increased risk of maltreatment compared to children of women who were not abused. Previous studies have provided conflicting results because of retrospective methods of obtaining data, poorly matched comparison groups, and inconsistent definitions of abuse.

We identified index girls who had been physically abused by reviewing the child abuse registry at Yale-New Haven Hospital (YNHH) from 1967-75. Comparison girls were matched to index girls by age, race, and SES and were chosen from the Emergency Room logs of children who presented with a medical illness during the same time period as the index girls and had no evidence of maltreatment. Girls were included if they subsequently give birth at YNHH. The medical records from 0-4 years of age of the first-born offspring of both groups were reviewed at YNHH and two other major health centers in New Haven to determine two outcomes: maltreatment (abuse or neglect) or endangerment of the child (based on a report to the hospital's abuse registry). All injuries were categorized as abuse, neglect, or accidental by two reviewers, one of whom was "blind" to the child's group status.

The final sample included 44 index and 44 comparison subjects and their 88 offspring. Of the 88 girls, 70% were black, 84% were on Title 19, and their mean age was 8.8 years at the time of identification. Offspring of index and comparison subjects did not differ significantly in gender, neonatal variables, or duration of follow up (mean = 38 months). Offspring of index subjects were more likely to have been maltreated (13.6% vs 4.8%, RR 3.0, C.I. =0.64,14.1) or endangered (22.7% vs 7.4%, RR=3.3, C.I. =0.98,11.3). The overall risk of having at least one of these adverse outcomes was significantly higher for the index offspring (29.5% vs 11.9%, RR=2.6, C.I. =1.01,6.71).

We conclude that children of women who were physically abused during childhood are three times more likely to be maltreated compared to children of women who were not abused.

Peak Serum Bilirubin in Normal-Sized Infants and Neurodevelopmental Outcome at Age 7: A Closer Look at the Collaborative Perinatal Study

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To investigate the association between neonatal bilirubin levels and subsequent cognitive and neurologic impairment, we analyzed data from the U.S. Collaborative Perinatal Project (CPP), a multicenter cohort study which enrolled 54,795 live born infants between 1959 and 1966. We restricted attention to white and black singleton infants with birth weights > 2500 g who survived ≥ 1 year and had neonatal bilirubin levels recorded. After adjustment for covariates using analysis of covariance, there was no association between peak bilirubin and IQ in either linear or threshold models in either blacks ($N=14{,}914$) or whites ($N=15{,}619$). Definite neurologic abnormalities at age 7 were found in 12/268 (4.5%) of children with peak bilirubin ≥ 342 μMol/L (20 mg/dl) compared with 1249/33,004 (3.8%) with lower levels (RR=1.2; 95% CI 0.7 - 2.1). The risk of *suspected* neurologic abnormality at age 7 increased gradually from 15% in those with peak bilirubin < 171 μMol/L (10 mg/dl) to 22% for bilirubin > 342 μMol/L (20 mg/dl); ($P < 0.001$), apparently because of a greater frequency of minor muscle and coordination problems and oculomotor abnormalities in those with higher bilirubin levels.

We conclude that high bilirubin levels in the newborn have little effect on intelligence or obvious neurologic abnormalities, but may be associated with an increase in subtle motor findings. Studies of the efficacy and cost-efficacy of treatment should be carried out before these findings are used to justify aggressive treatment of jaundiced newborns.

The Role of School Policies in Deterring Adolescent Tobacco Use

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Limiting access to tobacco and restricting its use in particular settings have become important means of deterring use among adolescents. This study tests the hypothesis that restrictive school policies are associated with decreased tobacco experimentation and regular use among adolescents. In 1989-90, and 1990-91, 3100 ninth graders in 32 school districts in Washington State completed detailed questionnaires about their past and present tobacco use; school superintendents in these districts responded to surveys requesting information about school policies affecting tobacco use. Policy effects were investigated with multiple and logistic regression analyses, controlling for school size and district-level socioeconomic status. Of the 32 school districts, 66 percent had well-communicated smoking policies, 94 percent prohibited smoking, 44 percent prohibited staff smoking, 34 percent had cessation programs for students, and 50 percent had cessation programs for staff. None had smoking prevention programs for students or staff. Nineteen of the districts (59 percent) had closed campuses, with students required to remain on school grounds during school hours. School districts with all or most of the restrictive policies in place showed many fewer students experimenting with or using tobacco regularly. The single most important policy was one that prohibited all smoking on school grounds. Closed campus policies were almost as highly correlated with decreased tobacco use. Districts that had been smoke-free for three or more years had fewer ninth-graders currently smoking than districts that had more recently prohibited smoking. In general, policies exerted less influence on smokeless tobacco use than on smoking. Also of note, punitive measures for policy violation had little effect on prevalence. Results of the study suggest that restrictive school policies are associated with decreased tobacco use among adolescents.

The Relationship of Temperament and Parent Expectations To Child Coping During Medical Procedures

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Medical procedures can be painful and frightening for young children. Recent investigations aimed at ameliorating pain have focused on its multiple etiologies, intervention to reduce it, and predictors of individual differences that facilitate and hinder coping. Children's temperament and parental expectations likely contribute to optimal coping, however, these variables need to be examined more systematically. 49 children (3-11 years old) were videotaped while undergoing a voiding cystourethrogram (VCUG). The child's distress and coping behaviors were coded from tapes, parents completed a temperament scale, and three other measures of fear, pain and coping were collected: parents pre-procedural rating of their child's fear, anxiety, and cooperation, technologists ratings of fear, pain, and cooperation following the procedure, and the child's self-assessment of "hurt" experienced using the OUCHER. Correlational analysis revealed that temperament was significantly related to behavior observed during the procedure. *Adaptable* children displayed more coping vehaviors ($p<.05$). *Difficult to distract* children expressed more pain ($p<.01$). *Impulsive* children asked more questions during the procedure ($p<.05$). Children predicted by their parents to be fearful and uncooperative were less calm and more physically resistant ($p<.01$). Technologist's blind ratings confirmed these patterns ($p<.002$). Children with high self-reported pain ratings expressed more verbal pain, were more physically resistant, and were rated by the technologists to be more fearful and less cooperative ($p<.03$). Together, these findings suggest (1) the child's temperament influences coping strategies, and (2) parents can provide accurate predictions of their children's coping abilities, thus, providing valuable information for the design of interventions used with the pediatric population undergoing painful medical procedures.

Non-Financial Barriers to Care

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Much attention has been paid to financial barriers affecting access to care but little is known about other barriers poor women perceive in obtaining health care for their children. To evaluate factors not related to health insurance coverage, we studied a random sample of mothers of 6-to-9-month-old infants ($N = 170$) who had received Medicaid during their pregnancies and lived in Guilford County, North Carolina. We assessed reasons for seeking medical care and attitudes towards private physicians (PMDs) and health department doctors (HDMDs).

We interviewed 128 (75%) of the mothers in the sample. Mean age was 23 years (range 15-41); 80% were black; 56% had more than one child. Respondents felt it was important to take their babies to the doctor to check on growth (98%), get immunizations (98%), talk about things that worried the mother (95%), and discuss behavior (85%), sleeping (75%) and feeding (71%). Mothers reported several barriers that they and friends had encountered: childcare for other children (65%), difficulty in getting to the appointment (52%), long clinic waiting times (48%), trouble finding a doctor who takes Medicaid (44%), not having a phone (38%), and problems with the health services themselves (13%). Few (35%) mothers took their babies to PMDs for regular care and most (59%) thought that PMDs would prefer *not* to see Medicaid families. However, the majority of mothers felt that PMDs were more competent than HDMDs (84%), spent more time with patients (69%), and were friendlier (62%).

Many of the barriers that mothers of Medicaid-eligible infants perceive are not related to insurance coverage. In addition, these women have very positive attitudes towards PMD care. Interventions to increase Medicaid families' use of PMDs might improve both the continuity and the quality of care for these children in areas such as the Southeast, where most health departments do not provide comprehensive care.

Medical Findings in Child Sexual Abuse Cases With Perpetrator Confessions

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Of 1456 suspected cases of child sexual abuse in females, there were 83 (5.7%) perpetrator confessions at the time of medical evaluation. The patients in the confession cases were significantly older than those in the non-confession cases (mean ages 7.70 vs 6.19 years; $p<0.001$). The confession cases were compared to an age-matched (by mean and distribution) subset of 563 non-confession cases for historical and physical examination characteristics. In all patients, anogenital anatomy was assessed by photocolposcopy.

In comparison with the non-confession group, confession cases demonstrated the following findings: (1) more Anglo victims ($p = 0.0239$); (2) more living with biologic families ($p<0.001$); (3) more referrals from law enforcement ($p<0.001$); (4) fewer with "other maltreatment" ($p<0.001$); (5) fewer multiple perpetrators ($p = 0.047$); (6) more brother perpetrators ($p = 0.004$); (7) more sexual contact (penile, vaginal and penile-vaginal contact, penetration and ejaculation; all with $p<0.001$); and (8) fewer abnormal general physical examinations ($p = 0.018$). There was no significant difference in the likelihood of abnormal genital findings between the two groups (confession group: 39.3% vs. non-confession group: 35.35%; $p = 0.509$). Of 22 patients with perpetrator confessions of penile-vaginal penetration, 4 (18.2%) had normal genital anatomy. Of 13 patients with allegations and confessions of only digital- vaginal penetration, 8 (61.5%) had normal genital anatomy. The latter findings demonstrate that children who have experienced vaginal penetration frequently have no demonstrable anatomic abnormalities.

Infant Health Care Utilization Predicted by Prenatal Care

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Prenatal care utilization is asserted to be associated with subsequent infant health care utilization. The purpose of this study was to correlate patterns of prenatal care with subsequent infant health care utilization in a sample of inner city women/infants.

Methods. Medical record review for infants born to mothers ($N = 209$) previously enrolled in a prenatal care/substance use case control study included number of immunizations by age, well child visits, hospitalizations and protective service referral up to age 9 months. Study cases were defined as infants born to mothers who registered for prenatal care after 28 weeks or had less than 4 prenatal visits. Controls included all other infants.

Results. 148 (71%) infant records were located and reviewed for cases (62) and controls (86). Significant results are presented in Table 1. Foster care referral and hospitalization did not differ by case or control status.

Infant Health Care Utilization by Maternal Prenatal Care

Outcome	Cases	Controls	Statistic	P Value
Birthweight (gms)	3038	3367	-3.48*	.0007
#1 immun by 4 months	32/62	70/86	13.56**	.0002
#2 immun by 6 months	14/62	57/86	25.84**	<.0001
#3 immun by 9 months	19/62	49/86	9.03**	.0020
3+ well child visits	36/62	70/86	8.53**	.0030
Protective Service Ref	18/57	11/79	4.97**	.0260

* t-test
** X^2

Conclusion. Infant health care utilization patterns may be established prior to birth. Inadequate prenatal care (<4 visits) may predict non-compliance with infant health care utilization. Intensive follow-up interventions are required for identified families.

Intranasal Midazolam as an Adjunct to Suturing Small Children

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Objective: Suturing can often stimulate intense anxiety and combativeness in young children. This study examined whether intranasal midazolam could aid suturing young children.

Methods: Children under 5 years old with simple lacerations requiring sutures were randomized to receive either intranasal midazolam (0.4 mg/kg), intranasal saline, or nothing prior to the procedure. All wounds were irrigated with sterile saline and locally anesthetized with lidocaine before suturing. Heart rate, respiratory rate, blood pressure, and oxygen saturation were monitored, and patients were scored at intervals for crying, movement, and struggle, each on a four-point scale.

Results: Fifty patients (age range: 9 - 59 mos., mean age: 34 mos.) were enrolled in the study. The study groups (midazolam, placebo, and control) did not differ significantly on age, site of laceration, length of laceration, duration of suturing, layers of suturing, or use of a papoose board. No significant differences in outcome were encountered between placebo and control groups, so their results were pooled ($n = 26$). The average increase in heart rate while suturing was 74% lower in the midazolam group than the placebo/control group (6.1 beats/min vs. 23.4 beats/min, $p < 0.005$). The mean crying score during suturing was significantly lower in the midazolam group (2.5 vs. 3.0, $p < 0.035$), while mean movement and struggle scores were also lower with a difference that approached significance ($p < 0.06$ for both). Telephone follow-up was achieved in 43 cases, and 12/19 parents in the midazolam group said that experience was better than expected compared to 8/24 in the placebo/control group ($p < 0.05$).

Conclusion: Intranasal midazolam proved to be a useful adjunct in suturing young children. Children with midazolam showed less increased heart rate and less vigorous crying, and more parents found the experience better than expected with midazolam.

Recent Trends in the Prevalence and Impact of Childhood Asthma

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Recent studies indicate rising morbidity and mortality due to asthma among children. We used the 1981 and 1988 National Health Interview Survey Child Health Supplements, which provide nationally representative data on 15,224 children ages 0-17 in 1981 and 17,110 in 1988 to examine changes during this period in (a) asthma prevalence; (b) measures of asthma severity; and (c) asthma's impact on a 32 item Behavior Problem Index.

The prevalence of asthma increased from 3.1% in 1981 to 4.3% in 1988 ($p<.0001$), with similar increases for children and adolescents, and both sexes. Increases occurred among Whites (2.7% to 4.1%, $p<.0001$) as compared to Blacks (5.3% vs. 5.1%, n.s.). Among those with asthma, there were fewer bed days reported in 1988 versus 1981 ($p<.06$), a lower rate of hospitalization in the last year (14% vs. 10%, $p<.02$), better overall health status (24% fair/poor vs. 12%, $p<.0001$), fewer school days missed (6% with >30 days vs. 3%), and a lower rate of extreme behavior problem scores (18% vs. 12%, $p<.01$). Similar reductions were seen among both Black and White children with asthma. Among all other chronic childhood conditions where the same questions were asked in both 1981 and 1988 there were no significant changes in prevalence or in indicators of severity. These results may be explained by a number of competing hypotheses: asthma prevalence is increasing, but largely due to less severe forms of the condition; less severe cases of the disease may now be labeled as asthma; improved management may improve functioning; or heightened awareness by parents concerning childhood chronic illness could lead to a greater identification of children with asthma. The latter hypothesis, however, would appear to argue that changes in prevalence should have been seen across a variety of the chronic conditions, which was not the case.

Neonatal Outcome in Infants With Evidence of Fetal Exposure to Opiates, Cocaine and Cannabinoids

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Meconium from 141 infants admitted consecutively to the full-term nursery was analyzed for metabolites of opiates, cocaine and cannabinoids. To maintain anonymity no personal identification was collected. Demographic data: 72% Afro-America, 82% medical assistance, 18% private insurance, history of drug use 18%, mean maternal age 24.2 yrs, mean birth weight 3234 gms±502, NAS 7%. Meconium data: 40% were drug free, cocaine present in 30%, opiates in 18% (cocaine &/or opiates 39%), cannabinoids in 40%. This study noted a higher prevalence of fetal drug exposure compared to 34% in an earlier anonymous maternal urine screen in this population. In 38 infants in whom urine toxicology was obtained for clinical indications, meconium was more sensitive than urine in detecting drug exposure (65.8% vs 31.6%). There was no significant difference between cocaine/opiate exposed & drug free infants in race, socio-economic status, maternal age, birth weight, head circumference, length, and apgar scores. Cocaine/opiate exposed infants had greater length of stay and increased maternal STDs during pregnancy, with a trend towards a higher percent with fetal distress. This study showed that a large percent of clinically normal infants had fetal drug exposure indicating that routine clinical assessment is insufficient in identifying drug exposed neonates. Since meconium is more sensitive and easier to obtain than urine it is a good measure of fetal drug exposure for prevalence and long term outcome studies.

A Comparison of the Development of Homeless and Domiciled Poor Children

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To compare the development of homeless and domiciled poor children, we administered the Revised Gesell Developmental Examination to 73/75 eligible children, 15-30 months, from two homeless shelters. They had no known developmental delay, were ≥36 weeks gestation, Hollingshead SES V, and on public assistance. To date, we have randomly selected 43 domiciled controls (same entry criteria) from our clinic. We determined demographic and medical factors, # of caretakers of child, and social risk factors (family size, single or adolescent parent, maternal education, Hx parental arrest, and Hx foster placement or abuse/neglect of mother or child).

In a multiple regression model controlling for demographic and medical factors, number of caretakers, and social risk, adjusted mean developmental quotients (DQs) were (homeless, domiciled): adaptive 81.1, 91.4 ($p<.001$); fine motor 84.6, 95.5 ($p<.01$); language 79.4, 88.2 ($p<.001$); gross motor 96.1, 99.7 (NS); personal-social 96.1, 101.7 (NS). Increasing social risk was associated with lower adaptive ($p<.01$), fine-motor ($p<.01$), language ($p<.05$), and gross motor ($p<.05$) DQs. Presence of a caretaker in addition to the mother was significantly associated with higher adaptive ($p<.05$) and language ($p<.05$) DQs. When coded as pass/fail in a logistic regression model, homeless children were more likely to fail the Gesell (adj. odds ratio = 17.4; 95% CI 1.8, 168). Higher social risk also was significantly associated with greater likelihood of failure.

Homeless toddlers have significant developmental delays compared to equally poor children, even when controlling for confounding factors. Numerous social risk factors and limited child-rearing supports are prevalent among homeless families, and we have shown that these are important negative influences on child development. In addressing the problems of development of poor children, high priority must be given to those who are homeless.

ABSTRACTS READ BY TITLE

Correlating CBC Profile With Infectious Outcome in 1009 Consecutive Febrile Infants Aged 0-8 Weeks Who Received Sepsis Evaluation

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The CBC is routinely performed in the evaluation of febrile young infants. To correlate CBC profile with infectious outcome we reviewed 1009 consecutive cases of febrile [rectal temperature >38°C] infants aged 0-8 weeks receiving sepsis evaluation [LP; CBC, blood culture; U/A; urine culture] during a 7-year period. 81 infants had serious bacterial infections [+SBI: 21 bacterial meningitis, 23 bacteremia, 29 UTI, 8 *Salmonella* GE]; and 928 infants were culture-negative for bacterial pathogen [−SBI]. Student t-test showed a significantly $>$ [$p < 0.001$] mean total WBC count [WBC] and absolute band count [ABC = total WBC count × % − bands] in those +SBI compared to those −SBI [the difference in mean % − PMN's between the 2 groups was not significant]. Receiver-operated-characteristic curves constructed for WBC and ABC showed ABC was the superior diagnostic test, with a significantly $>$ area under the curve [$p < 0.05$]. 44% of all infants had ABC <250/mm^3; this cutoff value had 93% sensitivity and 99% negative-predictive value for +SBI. By contrast the sensitivities for commonly-used WBC cutoff values of $>10{,}000$/mm^3, $>15{,}000$/mm^3, and $>20{,}000$/mm^3 were only 69%, 31%, and 13%, respectively, for +SBI.

Systemic Group B Beta-Hemolytic [GBS] Infections in Children: 75 Outpatient Cases in 13 Years

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We reviewed 75 consecutive cases of systemic GBS infection in children evaluated as outpatients. Patient ages ranged from 5 days-8 months [57 aged <2 months (75%); 18 aged 2-8 months (25%)]. Early-onset disease [EOD; <7 days old] occurred in 8 patients [10%], and late-onset disease [LOD] in 67 patients [90%]. There were 45 blacks [60%] and 30 whites [40%]; the male:female ratio was equal. Symptoms included fever [91%], irritability [83%], lethargy [77%], and altered-feeding pattern [59%]; symptom duration was <24 hours in 66 patients [88%]. On presentation, 25 patients [33%] were afebrile [8 with GBS meningitis], and 24 [32%] were not ill or irritable [6 with GBS meningitis]. Of 30 patients with GBS meningitis [40%] a significantly $>$ proportion [$p < 0.05$] had EOD or neutropenia [ANC <1500/mm^3]; other focal infections occurred in 18 patients [24%], including pneumonia [6 cases], cellulitis/adenitis [6 cases], osteomyelitis/septic arthritis [5 cases], and otitis media [1 case]. No patient required pressor therapy for hypotension; all patients survived. Systemic GBS infection in pediatric outpatients can afflict infants up to 8 months old, is $>$ common in blacks, can present without fever or compromised clinical appearance, and has a low mortality rate.

Normal Cerebrospinal Fluid Values in Infants 0-8 Weeks Old

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With no prior data on normal CSF values in full-term, healthy infants 0-8 weeks old, we studied 72 such cases with non-traumatic LP [<1000 RBC/mm^3], culture-negative CSF [bacteria and virus], and final diagnosis of non-specific febrile illness. [ANC = absolute neutrophil count; +2 S.D. defines the upper limit of normal for 97% of patients.] The WBC count was 0/mm^3 in 7 infants [9%]; and ≥ 10/mm^3 in 15 [47%] 0-4 weeks old compared to 7 [18%] 4-8 weeks old [$p < 0.007$]. The ANC was 0/mm^3 in 42 infants [58%] and ≥ 1/mm^3 in only 4 infants [5%]. The differences in mean WBC, %-neutrophils, ANC, and glucose level between groups were all N.S.; whereas the protein level was significantly $>$ in those 0-4 weeks old [$p < 0.007$]. Physicians can use these values to define "normal" CSF composition in infants aged 0-8 weeks.

Efficacy of Adrenaline-Cocaine [AC] Gel Topical Anesthetic For Dermal Lacerations In Children

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We evaluated the anesthetic efficacy of AC gel topical medication in 35 children with dermal lacerations of the face, lip, and scalp. AC gel was made by mixing 1.5 ml of conventional AC liquid [adrenaline 1:2,000; cocaine 11.8%] with 0.15 grams of methylcellulose [an inert emulsifying agent] to form a gel-consistency. Lacerations were located on the face [25 patients], outer lip [5 patients], and scalp [5 patients]; 12 lacerations were larger-sized [length >5 cm or depth >5 mm]. The average dose of AC gel applied/laceration was 0.35 ml [40 mg of cocaine]. Placement of 162 of a total 164 sutures [99%] did not elicit any pain; there were no adverse reactions with AC gel administration or complications of wound healing in any patient. No patient required supplemental lidocaine infiltration. Compared to all prior studies assessing conventional liquid topical anesthetics, this is the lowest average dose of cocaine used to anesthetize wounds and the highest rate of anesthetic efficacy documented. The AC gel preparation provides excellent anesthetic efficacy for minor dermal laceration repair in children. Compared to liquid topical anesthetics, increased viscosity of AC gel allows direct application of medication onto wound surfaces, requires a smaller total dose of medication, and eliminates risk for adverse reactions which can occur when liquid medication runs-off onto mucosal or ocular surfaces.

Carbamazine: A Fatal Interaction

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Carbamazine is a fairly toxic frequently used anticonvulsant. It is well known that erythromycin elevates carbamazine blood level and increases its toxicity. We are here reporting a fatal interaction. The patient was a four year old black male who had just began carbamazine for seizures. Carbamazine is a tricyclic antidepressant used as an anticonvulsant. Three weeks post onset of therapy the patient developed pharyngitis for which erythromycin was prescribed. Five days later the patient was admitted to the E.R. after a seizure followed by cardiorespiratory arrest. Laboratory examination revealed a platelet count of 12,000/mm^3(uL) and a carbamazine level of 22 μg/ml (122 μmol/L). He was resuscitated but subsequently it was determined that he had suffered a massive intracerebral hemorrhage. After 2 weeks in a respirator and 2 flats EEG,s 24 hours apart the respirator was stopped and he was pronounced dead. Thrombocytopenia and cardiac arrhythmia are pharmacotoxic effects of carbamazine.

The Use of Anesthetics for Invasive Medical Procedures in NICUs and PICUs

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Since the 1970s pain control for children has improved. It is unclear whether this change extends to neonates. The purpose of this study was to compare the use of anesthetics for invasive medical procedures in PICUs and NICUs.

The fellowship directors of 38 of all 52 (73%) PICUs and 31 of 51 (61%) randomly selected NICUs offering fellowship training completed a questionnaire about pain related to procedures. The centers surveyed (PICUs and NICUs) did not report using anesthetics often or always (regularly) for venipuncture (2%), intravenous cannulation (10%), suprapubic bladder aspiration (8%) or urethral catheterization (2%). Anesthetics were used significantly more regularly in PICUs than in NICUs for arterial line placement (66% vs 26%, $p = .001$), bone marrow aspiration (94% vs 64%, $p = .01$), central line placement (92% vs 68%, $p = .01$), chest tube insertion (95% vs 60%, $p = .001$), paracentesis (77% vs 27%, $p = .001$) and lumbar puncture (50% vs 7%, $p = .001$). The most commonly reported anesthetics were lidocaine, morphine and fentanyl. Behavioral techniques to control pain were used significantly ($p = .004$) more often in the PICU (42%) than the NICU (8%). The number of fellows in training and number of full-time faculty did not influence responses in either ICU setting.

We conclude that (1) for less invasive medical procedures few children in PICUs or NICUs receive any anesthesia and that (2) for more invasive procedures newborn infants receive significantly less anesthesia than older children. It is unclear why differences in the management of pain between older children and newborns persist.

Parenting Knowledge Among Urban Caregivers

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Caregivers bringing their children to large county hospital clinics for health care are assumed to have low educational levels and viewed as poorly informed on child care topics. To test this belief caregivers who bring their children to an appointment based full service clinic in a large urban county hospital were questioned on child care knowledge. The questionnaire consisted of 40 questions covering 10 child care topics and was administered to 54 caregivers after completion of their visit. The average age of the caregiver was 27.7 years old (range

16-51) with 96% black and 66.7% having 2 or less children. Most (68.5%) had completed high school and of these 32.4% had gone on to vocational school or college. Knowledge level was high with an average correct response rate of 78.6%. These results are contrary to what has been the general assumption regarding caregivers who use urban facilities. This data reflects a need to restructure current attitudes and educational efforts.

Pigmented Apocrine Hamartoma: Seen is Association With Chronic Sexual Abuse

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A case of pigmented vulvar lesions is presented which was observed in association with chronic sexual abuse. Gross examination of the lesions appeared most consistent with a sexually transmitted premalignant disease. Biopsy confirmed the lesions to be pigmented apocrine hamartomas. To our knowledge, these rare and benign tumors have never been described as pigmented.

Are Skull Radiographs Useful in the Evaluation of Asymptomatic Infants Following Minor Head Injury?

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Recent studies indicate that infants are at increased risk for skull fractures following head trauma. The purpose of our study is to examine the utility of skull radiographs in asymptomatic infants presenting after a minor head injury. We retrospectively reviewed the records of all head injured infants who presented to an Emergency Department between March 1990 and October 1991. During the study period 41 asymptomatic infants were evaluated in the Emergency Department and underwent skull radiography. The mean age of the study patients was 5.5±3.8 months, 54% were male and falls accounted for 90% of the injuries. The skull radiograms were normal in 30 patients, equivocal in two and positive for a parietal skull fracture in three infants. The three infants who sustained skull fractures were male, younger than three months of age and had fallen from heights not exceeding three feet. Computed head tomograms revealed no intracranial pathology in these patients. We conclude that all infants presenting following head trauma should undergo radiologic evaluation.

Are Routine Immunizations in the Emergency Department Realistic?

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We conducted a study to determine parental knowledge of their child's immunization status and the availability of an immunization record during the ED visit. Parents of 100 children presenting to the Loyola Pediatric ED were asked to complete a survey. The 100 parents were 30.2±0.9 years old and 81% were high school graduates. The children were 4.9±0.5 years old.

Parent said child was fully immunized=	89%
Parent knew exact number of child's immunizations=	20%
Parent kept a record of child's immunizations=	79%
Parent had the record available in the ED=	5%
Child has a regular site to receive immunizations=	94%

We conclude that a large number of children are underimmunized (11%). Although 89% of parents said their child was fully immunized, only 20% could accurately recall the exact number of immunizations their child had received and only 5% had the immunization record available in the ED. Since parental knowledge of childhood immunizations is poor and few parents bring an immunization record to the ED, it is impractical to administer routine immunization in the ED.

Cognitive and Motor Score Differences in At-Risk Infants

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The Bayley Scales are frequently used in high-risk infant follow-up. However, interpretation of differences in the Mental (MDI) and Psychomotor (PDI) Developmental Indexes is problematic. Herein, MDI/PDI differences are evaluated in terms of socioeconomic status/social support (SES-COMP Index), postnatal complications (PCS), and cognitive ability level (AL).

443 subjects were evaluated with the Bayley at 6 mo., 309 at 12, and 193 at 24 months. The SES-COMP and PCS were scored at enrollment. MDI/PDI differences were evaluated with a split-plot ANOVA, using SES-COMP and PCS quartiles, and 4 ALs.

No significant SES-COMP effects were noted. PCS score was influential at 6 months ($p = .05$), at 12 months an overall MDI/PDI difference was found ($p < .0001$), and no PCS effects were found at 24 months. MDI/PDI differences are inversely related to biologic risk early on with PDI > MDI. Main effects and interactions were found for AL and MDI/PDI differences at 6 mo. ($p < .001$, $< .004$), and at 12 mo. ($p < .001$, $< .04$). At 24 mo., there was a main AL effect ($p < .001$) and an AL × MDI/PDI interaction ($p < .0001$). Increased MDI/PDI discrepancies were associated with higher ALs, with MDI > PDI (M 3-14 pts); at lower ALs PDI > MDI.

MDI/PDI differences are not directly influenced by SES and social support, are affected by biologic risk factors early on, and are strongly related to cognitive ability level throughout infancy. Ceiling and floor test effects, correction for prematurity, and interrelationships between MDI and PDI are considerations.

Observer Agreement for a Method of Stool Assessment

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Interobserver agreement was determined for a proposed method of stool assessment. Stools from patients less than 3 years, hospitalized at The Hospital for Sick Children, were categorized as watery, loose, pasty or formed within minutes of being passed. Stools in the first two categories were defined as diarrheal stools, whereas the latter two categories were considered **not** to be diarrheal. Stool specimens were obtained from a convenience sample of 48 children with (52%), and without (48%), diarrhea. Nurses received training sessions and parents were instructed individually prior to each observation. Agreement was determined using the kappa statistic which measures agreement beyond chance. Group A consisted of 3 pairs of nurses in which each pair independently examind 10 stool samples from different children. Complete agreement was observed in this group of subjects. Group B consisted of 30 paired observations between nurses, where one of the two nurses was aware of the diagnosis of the patient from whom the stool was obtained. Observed agreement was 90% in this group and kappa was 0.78. Finally, agreement was determined between a parents' group and the second group of nurses. Observed agreement was 75% and kappa was 0.5. Kappa below 0.3 is considered to be poor, 0.3-0.6 to be fair, and greater than 0.6 to be good agreement. These results suggest that there is moderate to good agreement in assessment of stool appearance in young children, and stool appearance should be considered in assessments of children recovering from diarrhea.

HIV Testing in Pregnancy: What is the Evidence on Screening?

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A causal pathway is presented to help pediatricians determine whether their adolescent pregnant patients should undergo screening. Injection drug users, and those who are sex partners of those at risk of having HIV infection, should be screened in order to offer them interventions. However, fewer than 10% of physicians routinely obtain the necessary sexual and drug use history. Excess blood obtained at the time of prenatal screening or from infants during mass PKU screening tested anonymously has demonstrated that seroprevalence varies considerably between countries and even in different cities within the U.S. (0.2-14/1000). In high prevalence clinics, targeting groups for HIV testing using risk questionnaires has a sensitivity of only 50%, and routine testing has been advocated in such situations. A + HIV test is the detection of antibodies with a repeatedly abnormal enzyme immunoassay (EIA) and a confirmatory test (Western Blot or immunoflourescence). The combination test is 99.9% sensitive and 99.995% specific when performed under ideal circumstances. In an Ontario population (seroprevalence 0.3/1000), routine screening of pregnant patients would lead to six truly positive individuals identified for every falsely identified subject, whereas in an inner-city population in NE U.S. (seroprevalence 8/1000), 158 true positive individuals would be identified for every false positive individual. The negative impact of being false positive (labelling, anxiety) has to be weighed against the potential benefits to mother and infant in true positive situations. Where the ratio of true:false positives is high, centres should consider routine screening of pregnant adolescents.

Randomized Control Trial of X-Ray Ordering for Extremity Trauma Using the Brand Protocol

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Nine hundred and seventy-three patients (991 injury sites) were randomly assigned to have their x-ray ordered by either triage nurses using the Brand protocol (BP group, $n=492$), or by physicians using their own criteria (SP group, $n=499$), as in standard practice.

The primary outcome variable was proportion of x-rays ordered, 81.9% of the BP group had x-rays ordered compared to 87.1% of the SP group ($p=0.03$). The proportion of clinically significant x-rays was 40.8% in the BP group and 42.5% in the SP group ($p=0.21$). However, the BP group had 16 missed X-ray findings (3.3%) compared to 0 in the SP group ($p<0.0001$). Mean total time (± SD) spent in the emergency room was (ER) 3.65 (± 1.47) hours in SP group compared to 3.28 (± 1.66) hours in the BP group ($p<0.0001$).

The Brand protocol cannot be recommended for use alone in the pediatric population. Having triage nurses order x-rays does significantly decrease the total time patients spend in the ER.

Methods and Evaluation of Problem Based Learning: An Integrated Short Course for Second Year Medical Students

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Problem-based learning is an educational method which focuses on providing the student with the skill of effective clinical reasoning. Opportunities for students to formally learn and practice clinical problem solving early in their careers is limited. To introduce problem solving into the second year curriculum at USUHS, we designed a problem-based short course and attempted to assess short-term outcome. The elements of the course included: 1) training of faculty facilitators in problem-solving concepts, 2) student instruction in the methods of clinical reasoning, and 3) brief lectures and handouts to provide a preliminary knowledge base. Three concept areas of pediatrics: growth, neonatal transition, and fever in a young child were presented in separate sessions. The knowledge sessions were followed by small group interactions in which students solved clinical problems in the concept area. Discussions were led by a faculty facilitator who emphasized pertinent data collection in view of student-generated differential diagnoses. A prospective descriptive study was begun to assess outcome of the educational intervention. Students were graded in their ability to solve a clinical problem in an essay exam format. The essays were evaluated by the authors using a weighted 10 point answer key which gave maximal credits for logical and pertinent data collection and analysis. Results for the current academic year showed that most students grasped the problem-solving concept, with an average score of 7 points out of a maximum of 10. Student evaluations of the course format were favorable. Many students favored the problem-solving essay over a multiple choice exam. This format for teaching problem based learning is a complete package designed to be easily intergrated into the limited time pediatrics is allotted in pre-clinical years, and may be of value to other medical schools who are similarly time constrained.

Impacting on Parental Smoking During the Pediatric Visit

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The purpose of this pilot project was to compare two different antismoking messages given to mothers during their child's primary care pediatric visit.

Mothers received either the "Passive Smoking Message" (PSM) which informed subjects only about the negative impact of passive smoking on their children, or the "Maternal Smoking Message" (MSM) which described the risks of smoking for the mother herself. Group assignment was random.

One hundred mothers participated in the pilot project; 3 week follow-up data is available for 65. Subjects will be resurveyed for a 4 month follow-up. Subjects report greater motivation to change a health behavior if it will benefit their children rather than themselves, (62% v. 26%, $p < .001$). More mothers in the PSM group reported smoking cessation at 3 weeks compared to mothers in the MSM group. (15% v. 6%, $p=NS$)

These findings suggesting that the PSM message is a stronger motivator than the MSM message need to be replicated in a larger study, using a more objective biological endpoint, and for an extended period of time.

Parental and Patient Perceptions About Encopresis and its Treatment

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Encopretic children and their parents have misconceptions about the causes and treatment of this condition. We compared parent/child perceptions in responders and non-responders. Children followed for secondary encopresis in a multidisciplinary Incontinence Clinic from 1984-1989 were sent a parent/child questionnaire by mail, seeking opinions on this condition and its treatment. Results were compared using chi-square. Return rate was 60% (28/46). There were 20 boys and 8 girls, mean age was 7.3 years, mean time elapsed since diagnosis was 3.4 years, recovery rate was 35.7%. There were no differences between responders and non-responders on perceptions of causes, severity and usefulness of different treatment modalities. Parents did consider dietary changes more important than their children ($p<.01$). In children treated at our Incontinence Clinic, parent/child opinions about encopresis do not appear to influence prognosis. Physicians should consider that perceived causes and severity of encopresis and acceptance of treatment may not influence recovery rate.

Newborn Identification: Compliance with AAP Guidelines for Perinatal Care

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Discontinuation of routine footprinting for newborn identification has been recommended by the AAP and ACOG but not The National Center for Missing and Exploited Children (NCMEC). The objective of this study was to determine the extent of newborn footprinting conducted in U.S. nurseries.

Methods. A probability proportional sampling of U.S. hospitals with newborns nurseries (1004/5724) was surveyed by mailed questionnaire. Analysis included method of newborn identification, use of footprinting by number of deliveries, level of nursery care and geographic location, and need for infant identification and methods used.

Results. 711 of 1004 hospitals (70.8%) returned the questionnaire. Methods of newborn identification included footprinting (82.9%) saving cord blood sample for 3 to 10 days (43.4%); keeping a color photograph in the medical record (3.1%), and other (13%). Footprinting was used *less* frequently in New England and the Pacific states ($p<.0001$), Level II and III nurseries ($p=.001$) and in nurseries with a higher number of deliveries ($p=.0001$). Only 23 hospitals (3.4%) reported having to identify an infant within the 3 years prior to the survey; 16 of the 23 (69.6%) used footprinting for identification, but only 9 (39%) used footprinting alone. Only 6 of the 9 reported footprinting to be useful.

Conclusions. Newborn footprinting remains widely used in hospital in the U.S. despite the 1983 recommendations of the AAP and ACOG, and current availability of better methods of infant identification.

Psychological Impact of Neurogenic Bladder Surgery

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Incontinence secondary to neurogenic bladder frequently accompanies myelomeningocele. Dryness has become attainable via surgery. However, no systematic attempts have been made to evaluate the psychological impact. We used structured interview and standardized tests to assess impact in four children treated with the Kropp procedure (urethral lengthening/bladder augmentation). Changes in self-perception, behavior problems and social competence, family stress, and family functioning were assessed by comparing preoperative scores with those obtained a year later. Three children who attained dryness demonstrated improvement in self-perception of peer and maternal acceptance and self-worth. Positive change in parental perception of child behavior was also noted. There was no change noted on measures of family functioning. These findings suggest that achieving dryness through surgical procedure yields positive changes in self-perception. As these procedures carry the risks of significant morbidity and treatment failure, and require intense, possibly disruptive follow-up, further research in this area is warranted.

Why Patients Use The Children's Emergency Facility of a Large Inner-City Hospital for Non-Emergencies

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Possible reasons for attendance including immunization status, family constellation, age and education of the mother, source of income insurance coverage were determined for 99 children from 91 families arriving at the Pediatric Acute Care Center (PAAC). Only 11 children presented problems representing true emergencies. Lack of health care insurance (either Medicaid or private) was the only factor showing significant correlation with misuse of the PACC. No correlation was found between immunization status or other factors reflections past or present parental behavior and use of the PACC, but having a father live in the home and receiving income from work (as opposed to welfare) was associated with lack of health insurance and misuse of the PACC. Lack of complete immunization was associated with Medicaid coverage.

The data confirm that a lack of health insurance for the poor directs patients to emergency rooms for care. In addition, the criteria for receiving health insurance contribute to the social instability of inner-city communities by providing a counter incentive for families to remain intact and employed. Medicaid alone, however, does not improve the quality of preventive health care for poor children, given a chronic underfunding of quality ambulatory facilities in Brooklyn and the failure of physicians accepting Medicaid to immunize children.

Accuracy of Expectant Mothers' Predictions of Fathers' Attitudes Regarding Breastfeeding

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Fathers participate in the decision of feeding method regarding their newborn infants and can be effective promoters of breastfeeding. However, the perception of a negative paternal attitude toward breastfeeding will discourage some women from considering lactation. To determine if women can accurately predict father's attitude regarding breastfeeding, 268 pairs of expectant mothers and fathers enrolled in childbirth preparation classes at five hospitals in Houston, Texas, were surveyed. Descriptive statistics for general frequency distributions and chi-square analysis for determination of the association of each predicted and actual response were utilized. The study population was middle- to upper middle-class. The majority of subjects were white (mothers: 80%; fathers: 82%), married (95%), and had planned this pregnancy (77%). More mothers than fathers reported exclusive breastfeeding as their preferred feeding plan (70% vs 60%), while only 54% of partners both responded that they preferred breastfeeding. Mothers were correct in predicting their partner's response 56-83% of the time for each individual question. Overall, fathers had more favorable attitudes toward breastfeeding than their partners predicted. However, large numbers of fathers harbored misconceptions and negative attitudes toward breastfeeding; mothers' perceptions of these attitudes may impact against this choice. Efforts in childbirth preparation classes and other opportunities for breastfeeding education for fathers would assist parents in making informed decisions regarding infant feeding choice. Further education of fathers would foster a mutual appreciation among parents for the required effort and potential benefits of breastfeeding.

An Analysis of Adolescent Suicide Attempts: A Validation of the Expendable Child Measure

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The present study is an attempt to validate the Expendable Child Measure developed by Woznica and Shapiro (1990) as an instrument which differentiates between suicidal and nonsuicidal adolescents. Forty adolescents, ages 12-22, who were treated in psychotherapy at a Teenage Health Clinic were rated by their therapists on degree of suicidality and the Expendable Child Measure (ECM).

The ECM is a 12-item scale designed to assess the components of the expendable child syndrome, a cluster of feelings and perceptions reflecting a sense of being unwanted and/or a burden on the family.

Results of this study support previous findings (Woznica & Shapiro, 1990) indicating that suicidal adolescents were rated significantly higher on the ECM than were nonsuicidal adolescents (p<.001). These results provide further evidence of the validity of the ECM as a viable assessment measure in the area of adolescent suicide. The concept of expendability has important implications for the prevention and treatment of adolescent suicidality.

Fever Phobia: The Pediatrician's Contribution

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Fever phobia, the exaggerated fear of fever, is found among parents of all socioeconomic classes. Pediatricians may inadvertently contribute to fever phobia. To determine how MDs treat fever in their practice, we sent a self-administered questionnaire to a sample of members of the AAP who lived in MA. We asked pediatricians 1) how dangerous they believe fever is, 2) how they treat fever in their practice and 3) what types of educational intervention they use with families regarding fever.

One-hundred and seventy-two of the 234 (74%) eligible MDs returned the survey; 151 were completed. Respondents were 60% male and 75% of MDs practiced some form of primary or episodic care. Ninety eight (65%) believed that fever in and of itself could be dangerous to a child with 58 (60%) of these citing that a temperature of 104°F or greater could lead to complications such as seizures, brain damage or death. In practice, 108 (72%) always or often recommended treatment to reduce fever and 96 (89%) of the 108 did so at temperatures between 101°-102°F. One hundred and thirty-one (88%) respondents agreed that a sleeping child with fever should be left undisturbed. One hundred and twenty-one (80%) MDs always or often tried to educate families about fever during sick child visits yet only 38% addressed the dangers of fever to families.

We conclude that 1) many pediatricians believe that fever (with no underlying treatable cause) over 104°F could lead to serious complications and 2) most pediatricians educate families about fever predominately during sick visits. Pediatricians may be contributing to fever phobia by advocating contradictory messages to parents about fever, for example prescribing antipyretics for children with temperatures between 101-102°F while recommending that a sleeping child with fever be left undisturbed and by not fully addressing parental concerns about the dangers of fever during both well and sick child visits.

Common Beverages as an Alternative for Standard Oral Rehydration Solutions (SORS) in Developing Communities

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Previous studies show poor compliance and low availability of SORS for infantile diarrhea in developing communities. Various drinks have been used as substitutes. In this study 85 commercial beverages were analyzed for Na & K content and osmolarity, to see whether some may serve as an alternative for SORS.

	n	Na (mmol/L)	K (mmol/L)	osmolarity (mos/L)
non-carbonated	28	2.3±4.4	3.8±1.9	599.3±46.7
carbonated	23	1.9±5.2	2.0±2.2	586.5±116.4
natural juices	21	2.9±1.1	21.4±7.7	719.8±71.4
mineral water	9	0.4±0.8	0.4±0.1	23.9±7.3
vegetable juices	4	76.0±4.6	49.6±13.4	553.5±36.0
SORS		30-90	10-25	<330

We conclude that among many common commercial beverages only natural vegetable juices (water diluted 1:1) are probably appropriate alternative for standard oral rehydration solutions in infantile diarrhea in developing communities. This should be tested in future clinical studies.

Prenatal Care and Drug Use During Pregnancy

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Illicit drug use during pregnancy is associated with increased obstetrical and neonatal complications. We compared drug use in pregnant women who registered for prenatal care after 27 wks gestation or had <4 prenatal visits (cases) with that in women who had registered for prenatal care at <28 wks or had ≥4 visits (controls). 209 women were recruited, of which 204 (98%) agreed to substance use interviews. Urine toxicology screens were obtained on 169 (81%) mothers and 97 (46%) infants within 48 hours of delivery. Frequent drug users reported use of marijuana, cocaine, or heroin ≥2 days per week during this pregnancy or had a positive maternal or infant toxicology screen for these drugs. 25/81 (31%) cases and 20/128 (16%) controls were frequent drug users (OR 2.4, CI 2.1, 2.7, $\chi^2 = 6.8$, $p = .009$). Linear regression showed frequent drug use ($p = .05$) and unemployment ($p < .001$) to be correlated with case status, controlling for confounding variables (education, race, and marital status). Screening by detailed substance use history, toxicology screen, or both is advisable in pregnant women, especially those with less utilization of prenatal care.

The Effect of Mailed Patient Educational Literature in a Pediatric Practice

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This pilot study tested the effectiveness of informational handouts as patient educational tools. We mailed randomly selected families specific guidelines on the home management and warning signs of common pediatric problems: vomiting/diarrhea and cold/flu.

We then monitored phone calls over a two month period and mailed surveys anonymously to rate the helpfulness of these handouts. Between the 796 patients in the intervention and the 1792 patients in the control group, there was no difference in the percentage or nature of calls. Seventy-three percent reported that they had used the handout to help them with their child's illness. A majority of patients reacted positively to this form of education. We conclude that while direct mailing of information did not change phone call patterns, the limited survey results suggest that many parents perceive this information as useful.

Health Professionals' Beliefs and Attitudes About Attention Deficit Hyperactivity Disorder

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School nurses ($n = 88$), family practitioners ($n = 52$) and pediatricians ($n = 43$) enrolled in continuing education workshops were surveyed using the ADHD Beliefs & Awareness Questionnaire. All groups had similar knowledge about characteristics of the disorder, but differed on their understanding of assessment and management. Physicians had better understanding of management than school nurses, which emphasizes the need for physician-to-nurse communication about medication therapy. School nurses were more aware than family practitioners of the limited usefulness of the physical exam for diagnosis. We identified myths that health care professionals may still hold, including beliefs that a neurological exam may be a necessary diagnostic tool and that Ritalin causes growth suppression and has a "paradoxical effect" of calming rather than stimulating effect. We became aware that health professionals do not clearly understand the chronic nature of the disorder, how early the disorder can be detected, or the therapeutic range of Ritalin.

An Observational Study of Ambulatory Teaching in the Student Clinic

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An educational specialist (HGL) has spent about 100 hours observing faculty members and fellows teach students in the general pediatrics and adolescent clinics. He observed eight clinical teachers in their student-related activities. He observed some teachers for about 30 hours; others for shorter periods. Observations occurred by invitation or as part of a course in medical school teaching. The study purpose was to identify teaching objectives and advise on ways to attain these objectives. The clinic teaching method required students to interview and examine patients and provide preceptors with descriptions of their problems. Attending physicians then interviewed and examined the patients and worked with the students to develop and implement a management plan. The observer noted that preceptors put more emphasis on the students' ability to gather, organize and present information than on skill development or problem solving. Content taught varied, depending on patients seen. The authors suggest that clinical teachers avoid quizzing students about facts; they could improve skills training by observing students with patients, and instructing them on observing behavior and understanding patients' feelings. Use of simulated patients could standardize curricular content and improve student skills.

Evaluation of Every Febrile Infant Younger Than 120 Days of Age by Serum CRP Determination

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Management of the infant with fever is complex and controversial. The purpose of this study was to evaluate the serum CRP value for minimizing unnecessary procedures and hospitalization.

Serum CRP is a reliable marker for the presence of bacterial infection. Recently a new small detector for serum CRP was developed (Quick Turbo, Shino Test Co. Japan). Serum volume need for measurement is 10 µl, and it will take about 10 minutes to get the result. Using this detector, we prospectively examined serum CRP in all infants younger than 4 months of age who presented to our clinic between Dec. 1990 and Nov. 1991, with rectal temperature greater than 38° C.

Total number of patients enrolled were 77, and their age distribution and number were as follows; 8-30 days ($n = 15$); 31-60 days ($n = 26$), 61-90 days ($n = 15$) and 91-120 days ($n = 21$). These infants were divided 3 groups; 1) normal clinical signs with serum CRP $\leqslant 10$ mg/1 ($n = 40$), 2) abnormal clinical signs with CRP $\leqslant 10$ mg/l ($n = 9$), and 3) serum CRP > 10 mg/l ($n = 28$). Infants of Group 1 (52% of total) were observed in the outpatient clinic. Their clinical course was fair and fever subsided within 2 days. Infants of Group 2 and 3 were all admitted to the hospital, and 7 infants of Group 2 and 11 of Group 3 were considered the non-specific viral infection, respectively. There is no significant difference of percentage of the Group 1 infants among four age groups. We conclude that with the careful clinical observation serum CRP determination will be a valuable examination to manage the young febrile infant in the outpatient clinic.

Family Structural and Perceptual Factors Affecting Adaptation to the Onset of Diabetes in a Child

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Adaptation to chronic illness is a profound challenge to families. High stress levels may impact the ability of families to adapt to and integrate illness into everyday life and impede the child as he/she learns to cope with the disease. Data from 52 newly diagnosed diabetic children participating in a randomized trial of home vs hospital care currently under way at the Montreal Children's Hospital were collected from enrolment forms, Impact on Family Scale subscales, (mastery, personal strain, familial/social impact) and the Perceived Stress Scale. Using regression analysis we assessed the effects of eight predictor variables on levels of parental perceived stress at one month post-diagnosis. The variables used were: the number of siblings and adults at home, child's age, family income, parental assessment of mastery of the disease, personal strain, familial/social impact, and treatment group (home vs hospital care). In univariate analyses, the number of siblings and adults at home, age and treatment group were not significant in explaining stress levels, whereas personal strain and familial/social impact were highly significant (R^2, .182, $P = .002$; R^2, .142, $P = .006$). Income and mastery had modest explanatory power (R^2, .042; R^2, .091) and stress appeared to increase with low income and low mastery. The independent variables used in the final multiple regression models were 1) income, mastery, strain, sibling number and 2) income, mastery, familial/social impact. Overall R^2 and P values were .343, $<.001$ and .272, .002 respectively. Factors influencing model selection will be discussed.

Nitrate in Baby Food

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In order to avoid the risk of methemoglobinemia, parents are advised not to use water containing nitrate above the maximum contaminant level (MCL) of 45 mg/L nitrate (NO_3) in formula or food preparation for infants less than 6 months old. Currently no advice is provided regarding those baby foods (beikost) offered to young infants which may exceed the MCL for nitrate. The potential risk of methemo-globinemia occurring in beikost consuming infants is unclear. To determine this risk, a representative selection of 3 national brands of baby foods was purchased from local grocery stores. Samples of the baby foods were extracted with nitrate-free water and analyzed by ion chromatography. Results showed a gross mean nitrate level in mixed vegetables (63 µg/g), bananas (125 µg/g), carrots (137 µg/g), garden vegetables (141 µg/g), spinach (150 µg/g), squash (170 µg/g), green beans (293 µg/g) and beets (2225 µg/g). The amount of nitrate in one 4 oz. jar of carrots equals the nitrate content in 12 oz. of formula prepared with water at the MCL for NO$_3$ while the nitrate content in a 4 oz. jar of beets is equivalent to nearly 24 eight oz. bottles of formula prepared with water at the MCL for NO$_3$. To decrease the risk of methemoglobinemia, the introduction of high nitrate baby foods should be postponed until the infants are 6 months of age or older.

Vision Screening of Infants and Toddlers for Amblyogenic Factors Using Polaroid Photoscreening

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The difficulty of detecting amblyogenic factors including strabismus, refractive errors and opacifications of the ocular media by physical examination of infants and toddlers frequently results in a delay of diagnosis and treatment. In order to improve the ability of primary care providers in a child health continuity clinic (CHC) to correctly identify amblyogenic factors requiring referral to ophthalmology, a pediatrician and pediatric nurse were trained in the use of a polaroid photoscreening camera. The data obtained from polaroid photoscreening of 98 healthy CHC infants, 6 to 18 mos, without previously suspected visual problems were compared to a group of 107 high risk infants evaluated in the pediatric ophthalmology clinic. The results indicated a sensitivity of 75% and a specificity of 92% among those infants who received comprehensive eye examinations by the CHC pediatric nurse or pediatrician. These results compared favorable with sensitivity/specificity rates of 87% and 89% respectively for patients from a high pathology population examined by 2 orthoptists in the pediatric ophthalmology department. The study suggests that polaroid photoscreening is an effective screening device that can be used by pediatric primary care providers to screen for amblyogenic factors in the pre-verbal child.

Are Nitrates Concentrated in Human Milk?

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Pregnant and lactating women are advised not to consume water with a mean contaminant level (MCL) for nitrate > 45 ppm. To determine if the nitrate content of breast milk is influenced by the nitrate content of water consumed, 20 women breastfeeding infants > 6 mos old at least twice a day, were enrolled in a 3 day crossover study. The women were asked to drink a minimum of 1500 cc of the water which contained 0 ppm nitrate on Day 1, 45 ppm nitrate on Day 2, and 100 ppm nitrate on Day 3. A daily diet record was kept of all foods and beverages consumed to determine dietary nitrate intake. Infants breastfed on Days 1 and 2 but received an alternate milk source on Day 3. At the end of each study day, the mothers collected and froze breastmilk and urine samples. The analysis of breastmilk and urine for nitrate was done by a modified cadmium column reduction methodology. The results showed the mean total nitrates consumed in the *diet* and study *water* respectively were 46.6 mg and 0 mg on Day 1, 68.4 mg and 99.7 mg on Day 2, and 58 mg and 214.1 mg on Day 3. The mean nitrate concentrations of *breastmilk* and *urine* respectively were 4.4 mg/l and 35.8 mg/l on Day 1, 5.1 mg/l and 66.0 mg/l on Day 2, and 5.2 mg/l and 83.5 mg/l on Day 3. Women consuming water with nitrate concentration ≥ the MCL do not produce breastmilk with elevated nitrate levels ($p > 0.05$).

Telephone Consultation in Pediatric Ambulatory Service

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A computerized system of telephone consultation is being experimented at the Paediatric Ambulatory Service of Policlinico A. Gemelli of Rome. Twenty monothematic cards contain a series of questions intended to evaluate the child clinical conditions thus allowing to select the different cases according to their gravity on the basis of conventional scores corresponding to the different answers (yes/no) given by the child parents. This way, the system allows also to establish the medical check-up urgency which may be: immediate; within the next 24 hours; scheduled in the paediatric office. The paediatric pathologies taken into consideration concern: fever; headache; cough; wheezing; asthma; urinary tract infections; abdominal pain; vomiting and diarrhoea; head/nose/eye traumas; convulsions; burns; sunstroke; wounds; animals and insects bites; sprains; articular pain; ingestion of foreign body and poisoning. The system has been implemented with large diffusion DBMS running on a PC with at least 640 K of RAM and 20 MBIT HD. Thanks to its flessibility and simplicity, the programme allows all necessary changes to be easily carried out and can be used also for didactic purposes.

Overbundling and Overheating: Can They Cause "Fevers" in Neonates?

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The effect of bundling and ambient heat on newborn temperature has not been systematically studied. We hypothesized that bundling and warm environments can elevate infant temperatures significantly.

We assigned 19 well term newborns over one day old to either a control group (in 1 blanket; 24°C room) or treatment group (5 blankets and hat; 27°C room). Rectal probe and skin temperatures were monitored over a 2½ hour period.

There were 8 control and 11 experimental infants. The mean change in rectal temperature after 2½ hours was −.04°C in controls and +.57°C in the treatment group ($p<.0001$, t-test). Temperatures in the treatment group rose, after an initial lag, at a linear rate of .41°C per hour without a plateau. Two infants reached 38.0°C.

We conclude that bundling and warm environments significantly affect infant body temperature which can reach the "febrile" range. In view of these findings, physicians treating newborns with elevated temperatures should ask about bundling and environmental conditions to differentiate endogenous from exogenous "fevers."

Pediatric Resident Support Group: Review of a 7 Year Longitudinal Experience

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Resident support groups have been proposed as one important means of dealing with stress in residency training. We examined our experience with a pediatric resident support group which has met continuously over the past 7 years. A semi-structured anonymous questionnaire was sent to all current and past residents (N = 57). Results were analyzed from 47 completed questionnaires, (80% response). It was found that residents unanimously valued these weekly lunch meetings comprising residents at all levels. They felt it provided a safe setting to express thoughts and feelings about stressful aspects of training. Peer support promotes a sense of caring and cohesion within the residency program. The perceived value of the group increased after completion of training.

Factors which account for the success of this group include a convenient meeting place and time, provision of lunch, and an open agenda with strict confidentiality. The co-leaders establish consistent boundaries, offer comments, and assist in the transition each year.

We conclude that a resident support group with the format described above is highly valued by residents. It should be readily reproducible in other training programs.

Adolescent Health Services in North Carolina's Local Health Departments

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One in five adolescents suffers serious health problems, and many others are at high risk for school failure, unprotected sexual intercourse, or substance abuse. Comprehensive and preventive health services are a means of preventing these problems, but the degree to which these services are available to adolescents is not well known. We surveyed local health departments in all 100 North Carolina counties about health services provided to 10-19 year old adolescents. Approximately 21% of North Carolina youth received at least one health department service in 1990. The majority (85%) of local health departments provide health education services in public schools. Thirty-four health departments have programs or services designed specifically for adolescents. Adolescent programs are most commonly located in high schools (21 health departments), middle/junior high schools (20) and at the health department (20). Programs most often target adolescent sexuality (33), pregnancy (22), parenting (18), and self-esteem (17) issues. Most are staffed by nurses (25) and health educators (26), and rely on state and local funding. Only seven health departments provide comprehensive adolescent health services; four do so in school-based clinics and three in health department clinics. All seven comprehensive programs and only 22 out of 27 less comprehensive programs reported strong organizational linkages between their county health department and other service providers in their community. Few counties in North Carolina provide the preventive and comprehensive health care needed to promote the health of North Carolina's youth. Community-wide participation and support is needed to assure adequate access to comprehensive health care for adolescents in the public sector.

HIV Prevention in Comprehensive Adolescent Health Services

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Preventing HIV and other sexually transmitted diseases is a critical priority for adolescents' health. More than 50% of all adolescents have had sexual intercourse, and most do not regularly use barrier contraceptives. Comprehensive or integrated services are often advocated as a means of ensuring that youth have access to the broad range of services they need. However, the degree to which comprehensive adolescent services address HIV prevention and testing, or target services to adolescents with HIV (or at risk for HIV) is not known. In 1990-91, we identified, validated, and surveyed a national census of 660 sites providing comprehensive or integrated health services to adolescents in the US. Of the 456 programs (69%) responding to the survey, 90% provide HIV education on site and 92% provide other types of health education; 43% (187) of programs target prevention of unsafe sexual activities. However, these were no more likely to provide family planning, contraceptives or HIV testing on site than other programs. Only 64 programs target services to HIV positive youth. These programs were more likely to provide HIV testing (66% vs. 42%; $p<0.001$) and to provide contraceptives on site (73% vs. 54%; $p=0.004$). However, 27% of these programs did not provide contraceptives on site. Of programs targeting HIV positive youth, 39% were in HIV epicenters and most of the others were in states with MCH adolescent health coordinators. Programs targeting unsafe sexual activity and/or HIV positive youth were three times as likely to be in community-based settings than other adolescent health programs. Most adolescents do not have access to comprehensive health services. Since many adolescent comprehensive services do not provide contraceptives on site, most adolescents do not have access to optimally effective HIV prevention.

Early Increase in Hemoglobin After Mild Acute Childhood Infections

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Data on changes in hemoglobin concentration in the course of mild acute infectious illnesses in childhood are sparse. We evaluated such changes between the time of diagnosis and 3 to 33 days later (mean 12; SD 9) in 70 children (37 boys, 33 girls), ranging in age from 3 months to 10 years (mean 22 months). Follow-up hemoglobin levels were obtained within the first month after recovery at times when children were free of apparent illness and had had no fever for at least 3 days. The most frequent diagnoses were otitis media (17), viral upper respiratory tract infection (15), pharyngitis (7), gastroenteritis (7) and fever without a localizing source (7). Temperature of >38 C was recorded in 58 of the children. Mean hemoglobin concentration at the time of diagnosis was 10.1 g/dl (SD 1.1; range 7.3 to 13.9), and at follow-up was 10.7 g/dl (SD 1.1; range 8.4 to 13.2) ($p<0.001$, paired t-test). Of children with initial hemoglobin concentration <10.5 g/dL ($n=39$), 82% had values <11 g/dL at follow-up. We conclude that although an increase in hemoglobin concentration of about 0.6 g/dL is to be expected in the early period following mild childhood infections, children found at presentation to be anemic are likely to remain so after recovery. (This work was published in Hebrew in *Harefuah*, 1991; 120:651-653.)

Impact of Formula Advertisements and Other Factors on Initial Infant Feeding Choices

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A health care goal in the U. S. is to increase the rate of breastfeeding. We studied the association of formula advertising and other factors with initial feeding decisions. Subjects ($N=232$) were recruited within 36 hours of giving birth. Of mothers surveyed, 200 (87%) reported seeing formula ads but 153 (66%) reported seeing ads for brands not being advertised directly to the public. Thirty-six percent reported that the advertised message was to feed a new baby formula, 29% human milk, and 34% both. Chi Square analysis of the data showed that a father in the home ($p=0.0004$), being married ($p=0.0009$), and a planned pregnancy ($p=0.008$) were positively associated with breastfeeding. Other significant associations with feeding behaviors included ethnicity and maternal education. Only 31 (13%) stated that ads influenced their feeding decision. Although 60% of mothers stated that breastmilk was best for new babies, only 36% planned to breastfeed. Those who stated that human milk was best were not as likely to breastfeed as those who stated that formula was best were to formula feed ($p<0.0001$).

Norplant: Expected Patterns of Use in Teens

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We surveyed members of the Society for Adolescent Medicine and the American College Of Obstetrics and Gynecology about their attitudes regarding Norplant in teens.

Results: 204/383 (54%) responded: 93 pediatricians (PED), 74 gynecologists (GYNE), and 37 others. 33 physicians saw only teens in their practice. This group was 88% PEDs and 55% female. 120 physicians saw <50% teens in their practice, and were 68% GYNE and 78% male. Comparing these 2 groups, the former saw more poor patients (32% vs 15%, $p<0.002$); were more likely to see a role for Norplant in teens (96% vs 76%, $p<0.002$); and were more willing to use it for "any teen who chooses it" (45% vs 21%, $p<0.017$). The latter group was less likely to let teens consent ($p<0.019$); more likely to agree that Norplant should be used by GYNEs only ($p<0\ 0001$); and had been targeted more often by Norplant representatives (64% vs 18%, $p<0.001$).

Conclusions: Physicians with the most experience in adolescent medicine are most likely to use Norplant in teenagers, but are least likely to be targeted by Norplant producers Market forces, not medical expertise, many determine how this new technology is used.

The Role of the Prenatal Pediatric Visit in Pediatric Residency Training

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A survey titled "The Prenatal Pediatric Visit in Pediatric Residency Training" was conducted to determine the scope of the utilization of PPV's as a learning experience during pediatric training programs. The survey was mailed to 249 Pediatric Residency Training programs. After two mailings, a 52% response (129/249) was achieved. The results of our survey indicate that a small percentage of pediatric training, programs have their residents conducting PPV's (26%; $n=129$). In these programs, PPV's are conducted by the residents for the following reasons: 1) Education and counseling, 2) Developing an early continuity relationship with the family, and 3) Data gathering.

Residents in the majority of programs are *not* conducting PPV's (71%; $n=129$). Many programs identified Logistics as the primary reason why their residents were not doing PPV's. Difficulty scheduling, organizing and insufficient time were common responses related to this problem of Logistics. Thirty-nine percent of the *programs responding to the survey* ($n=129$) do offer formal training for their residents related to PPV's. Seventy-three percent of *programs whose residents do PPV's* ($n=33$) formally train their residents to conduct the visits. This training occurs primarily through Conferences/Lectures and Reading materials.

The PPV is recommended by the American Academy of Pediatrics for all expectant families. Pediatricians can develop the expertise during their training that will help them to ultimately be able to comfortably conduct PPV's with their expectant families.

Folk Beliefs and Health Practices Related to Children Seropositive for HIV Infection in an Urban Lower Income Population

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How and why a family chooses between various available health care services has received extensive attention in the literature. Personalized supports networks of family, friends, and church, are recognized as powerful influences in health care decisions. The purpose of this study was to explore folk therapies being utilized by the caretakers of children who are seropositive for the HIV virus.

The project design utilized an ethnographic style wherein 10 primary caretakers of seropositive children consented to an audiotaped interview. Open-ended questions elicited information about folk medies, the meaning of HIV positive test result, it's causes, and ailable treatment anthropologist.

The findings are categorized as follows: (1) Demographics, (2) Gen- al Health Practices, (3) Understanding of AIDS, (4) Response to hild's Diagnosis, (5) Social Isolation, (6) Illness Progression.

This study found that while folk therapies were utilized for illness general, they were not adopted specifically for HIV infection. A ossible explanation is the experienced isolation of caretakers who ar the diagnosis will result in social ostracism. One of the conse- uences of this isolation is lack of information about the availability f folk therapies for particular condition.

Physicians and the health care team need to be aware of the expe- enced social isolation and take a more supportive role encouraging pen communication with their patients. This may improve hysician/patient relations and increase compliance with medical erapy.

ardiac Nondisease Revisited: Is there Morbidity Associated with an nocent Murmur?

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Objective: Some parents of children with innocent heart murmurs ay think that their child's heart is abnormal and restrict the child's ctivity. This study was designed to determine the frequency of this isperception.

Method: Parents of 61 children with innocent murmurs were inter- iewed by telephone one to five years after their child's evaluation by pediatric cardiologist to ascertain whether they had any anxiety bout their child's cardiac status and whether any of the children's ctivities were being modified or restricted. The children had been etween 5 and 15 when referred to the Pediatric Cardiology Division t the University of Michigan for evaluation of a murmur; all had in- ocent murmurs.

Results: Eleven parents (18%) expressed some degree of concern hat their child's heart was not completely normal. None were restricting their children's activity or "watching the child more closely." nly a report of being less than "very satisfied" with the cardiologist's valuation was associated with persistent parental concern (Chi quare; $P<.005$). There was no association with parental education, amily history of heart disease, source of referral (child's regular phy- ician or other) or if the evaluation included echocardiography.

Conclusion: Some parents of children with innocent murmurs per- eive that their child's heart is abnormal. Follow up by primary care hysicians after referral for evaluation of a murmur may help to pre- ent parental misunderstanding.

he Role of the General Pediatrician in the Care of Children With erious Heart Disease

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Objective: Medical care of children with serious heart disease in- ludes tertiary care by pediatric cardiologists and primary and sec- ondary care that could be provided by a general pediatrician. This study evaluated the involvement of general pediatricians in the health care of this group of children with a complex chronic illness and the factors that influence it.

Methods: Questionnaires were administered to the parents, primary care physicians and cardiologists of 91 children with heart disease who were receiving care at the C.S. Mott Children's Hospital of the University of Michigan. Data were obtained regarding utilization and attitudes from the three groups of respondents.

Results: Use of a generalist was reported by more than 80% of parents for well child care, minor illnesses or if the child had a high fever. Less than 50% had gone or would go to their primary care physician to have cardiac drugs checked, to discuss the psychological or financial aspects of having a child with a serious illness, or if the child seemed "really sick." The attitudes held by parents and the behaviors and attitudes of the physicians that were associated with utilization will be presented.

Conclusion: General pediatricians should clarify with parents and subspecialists the role they wish to play in caring for children with medically complex illnesses.

Injury Related Death and Disability: Issues for Pediatricians

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Over 22,000 children die annually from injuries. Of these deaths greater than two-thirds happen to children 10-19 years of age. An additional 30,000 children suffer permanent disabilities. While little is known about short or long term effects on peers from the death or disability of a friend, children tend to feel vulnerable and upset following such pivotal events. The loss or death of a close friend might trigger increased risk taking behaviors, nightmares, depression, anxiety, and attentional difficulties. In spite of the serious implications of these tragedies, the impact of the death or disability on the patient's friends, classmates, and extended family goes largely unattended. We developed a multidisciplinary team to provide support and education to schools and communities and to develop culturally sensitive strategies to respond to the most frequently asked questions and concerning issues arising in school and other community settings. Questions from school personnel include the following: who to tell, how and what to tell, role of school personnel, funeral and hospital attendance, memorialization, and duration of contact and support. Children's questions are directed towards details of the injury and subsequent medical intervention, how they can avoid a similar tragedy, and how their friend was cared for. Pediatricians are in an excellent position to assist children, families, and school personnel understand and cope with this high prevalent, catastrophic event. In addition, injury and violence prevention may be suitable topics at school visits.

The Pediatrician's Private Office as an Ambulatory Placement in a Clerkship Rotation: Clinical Clerks' Opinions of the Learning Experience

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In an attempt to enrich the ambulatory component of the University of Toronto pediatric clerkship, 35 university-affiliated pediatricians agreed to be preceptors for clinical clerks based in their private offices for a 2 week rotation. 107 students (43% of the 1991 graduating class) were randomly allocated to pediatricians' private offices; the other students to a hospital-based ambulatory experience in the emergency or medical outpatient departments. The clerks' opinions of the eucational value of the ambulatory experience were elicited by questionnaire (80% response rate).

82% of those assigned to a pediatric office rated this as a very positive overall learning experience compared with similar positive evaluations by 78% and 38% of students assigned to emergency and medical outpatients, respectively. 90% of students reported a good or excellent experience in the assessment and management of common pediatric problems and 85% in the delivery of well-baby and well-child care. More than 2/3 of clerks felt that the office experience provided a good or excellent opportunity to develop interviewing and physical examination skills. 85% of clerks reported that they saw an appropriate number of patients to meet their educational objectives. Fourth year examination results indicated no specific differences among the clerks assigned to the various ambulatory settings.

Our data shows that an ambulatory rotation in a community pediatrician's office is a valuable and relevant learning experience for clinical clerks.

Do NYC's Children Have a Medical Home? Assessing the Content and Delivery of Pediatric Ambulatory Care

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Studies have documented that primary care can make a difference in improving the health status of children. In NYC 800,000 or 40% of children are poor. Hospitals and community clinics are the major source of ambulatory care for these children, providing 3.3 million visits a year.

A survey to determine the extent to which these clinics provide primary care was mailed to pediatric directors of all 105 hospital and community clinics in NYC. The questionnaire was designed to assess the extent to which the essential elements of primary care are in place and to identify obstacles to providing primary care.

60% of the questionnaires were returned and site visits were made to collect missing data. Preliminary results indicate that in 53% of the sites, patients see the same provider 90% of the time. Only 48% of the providers offer 24 hour phone coverage. Parents who use clinics that do not provide phone coverage have no option but to seek advice in an emergency room.

The findings describe some of the difficulties encountered in providing primary care and will be used to develop strategies to improve child health services in NYC.

The Sequestered Ones: A Family With Five Children Isolated from Society

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The report reveals how child abuse and child neglect may not always adhere to traditional measures of evaluation. We describe in detail the physical, developmental, behavioral and social effects in five siblings, 11 months to 7 years of age, who for personal and religious reasons were conceived, delivered, and reared without any contact with the outside world.

Remarkable lacunae in social skills, speech, interpersonal relationships, and motor development (including peculiar locomotion) were documented using photos and videotapes to establish baseline data with which future progress could be compared.

A facile prognosis for these children and their parents cannot be derived from present standards of medical and psychological assessment, nor is there any convenient method to assess what may have transpired without active intervention or what deleterious effects our intervention may have on the future development of these five children.

Keeping Heads Above Water in the Midwest

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Drowning is the second leading cause of unintentional injury death in US children. Rates are highest in sunbelt states (SBS); where private pools are the most common site and prevention has focused on pools. We suspected that many childhood drownings in the midwest (MW) occur in other sites. Charts of all 43 children admitted to CMH with submersion injury (SI) in 1985-1990 were abstracted, and county (CC) and regional mortality data were obtained.

51% of the CMH victims were <3 yo; 25% died or survived impaired. Sites were: private pools (PVT pools, 35%), bathtubs (BTB, 28%), public pools (PB pools, 19%), freshwater (FW, 9%), and buckets (BUC, 7%). SI site was related to age: BTB ≤1 yo, BUC <3 yo, PVT pool <5 yo, PB pool/FW ≥5 yo. BTB were generally urban; PVT pools, suburban/rural. No BTB SI was insured; no PVT pool SI was on public aid. Supervision, swimming ability and/or flotation devices were documented in some cases. Compared to childhood drownings in SBS, % PVT pool is low in CC, WI, and MN.

Conclusions: Many SI occur outside PVT pools. Risk is related to age, social, and environmental factors. Drowning prevention in the US must target several risk patterns.

Self-Concept and Alcohol Use in Black Elementary School Children

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Substance use prior to age 15 predisposes to substance abuse. However, little is known about the risk factors in preadolescents. We interviewed 355 black fourth and fifth grade students to test the hypothesis that children with low self-concept are more likely to have had problem alcohol use (PAU). Children were interviewed privately at their homes. PAU was defined as: drank without mother's permission, drank almost daily, has been drunk, has been in trouble because of drinking, or drank two or more drinks in one day. Self-concept, family income, and willingness to risk injury were assessed. At least one PAU behavior was reported by 14%. Multiple logistic regression analysis revealed two factors significantly related to PAU: low self-concept (odds ratio [OR] 2.75; 95% confidence interval [95% CI] = 1.23,5.95), and other substance use ([OR] = 5.16; [95% CI] = 2.27,11.7). Gender, willingness to risk injury, and family income were not significant risk factors.

Self-concept may play a role in the onset of problem alcohol use in black inner-city children.

Screening for Lead Poisoning by Fingerstick: A Reasonable Alternative?

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Evidence of adverse effects of lead at concentrations previously thought safe prompted the CDC to lower the cut-off for defining lead poisoning for an individual child to 0.72 μmol/L [15 μg/dL]. This places virtually all children at risk of lead poisoning and underscores the need for a fingerstick screening test for lead poisoning that is accurate at lower levels. This study is a comparison of the false-positive rate of lead screening methods using fingerstick specimens, compared to the "gold standard" of lead concentrations in venous blood. The following tests were performed sequentially from a single fingerstick on children (N = 753) presenting for routine pediatric care at an urban clinic: Zinc protoporphyrin (ZPP), and lead analyzed from blood collected by capillary tube (CAP) and absorbed onto filter paper (FP). A venous specimen was obtained immediately if ZPP was ≥ 0.62 μmol/L [35 μg/dL] or later if either fingerstick lead result was ≥ 0.72 μmol/L [15 μg/dL]. Venous specimens were obtained from 334 (75%) of the children with elevated screens. The correlation with venous lead concentration for each of the two fingerstick lead tests were comparable (Pearson r = 0.77 CAP; 0.75 FP). Nearly 1 of 3 elevated fingerstick tests by either CAP (28%) or FP (32%) in this population was a false-positive result. A significant false-positive rate should be anticipated for any fingerstick lead test, since the cut-off for defining lead poisoning in an individual child approximates this population's mean value (0.68 μmol/L [14 μg/dl] CAP and 0.77 μmol/L [16 μg/dL] FP), and the standard error for determination of even venous lead levels exceeds 0.10 μmol/L [2 μg/dL]. Consequently, either of these fingerstick tests is a reasonable alternative to venous testing.

Racial Differences in Ambulatory Care Access and Utilization Among Adolescents

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Racial differences in health care delivery exist for children and adults, but little is known about adolescent access. We evaluated data from the 1988 National Health Interview Survey on Child Health to test the hypothesis that adolescents of different races would have similar use patterns when insurance and income were held equal.

Despite worse reported health status, blacks (1.8) and Hispanics (1.7) made fewer annual doctor visits than whites (2.6). Higher proportions of blacks (16%) and Hispanics (28%) than whites (11%) were uninsured (p<.001). Minority adolescents were more likely than whites to have public clinics as their source of routine care (p<.001) and were less likely to have continuity between sources of routine and acute care (p<.001). After multivariate analysis to adjust for variables including health status, income and insurance, Hispanic-white differences equalized, while black-white differences persisted for both doctor visits and continuity of care. We conclude that universal health insurance would improve but would not eliminate the racial inequities in adolescent health care use and access.

Evaluation of AIDS Knowledge in an Underserved Pediatric Population

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An HIV/AIDS knowledge survey was administered to 25 mother-child dyads in the waiting room of the King-Drew Pediatric Clinic by bilingual facilitators during the summer of 1991. After the Magic Johnson announcement (MJA) that he was HIV(+) a second survey was undertaken. Nine Black and 16 Hispanic dyads with children ranging from 10 to 15 years of age were included in each survey.

In the initial survey, 6 of 9 black mothers (66.7%) and 6 of 9 black children (66.7%) achieved a passing score In Hispanics, 10 of 16 mothers (62.5%) and 6 of 16 (37.5%) children achieved a passing score. In the second survey 8 of 9 (88.9%) Black mothers passed while only 4 of 9 (44.4%) Black children passed. Both Hispanic mothers and Hispanic children scored the same as did those in the first survey.

Although statistical significance was not achieved at the .05 level these data suggest an increase in HIV/AIDS knowledge among Black mothers after MJA which was not evident among Black children, Hispanic mothers or Hispanic children. Also suggested is the need for more Pediatric and adult AIDS education in Minority populations.

Cognitive and Behavioural Sequelae of the Hemolytic Uremic Syndrome (HUS)

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Objective: To examine whether an acute episode of HUS has an effect on later central nervous system functioning.

Methods: Case-control study of 22 patients with HUS in childhood, with no known learning disability before the onset of HUS, and 22 controls matched on age, gender, first language, and socioeconomic status. A researcher unaware of the case or control status administered tests of cognitive ability, behaviour, and academic achievement.

Results: HUS patients had numerically lower cognitive and achievement scores and higher behaviour problem ratings than their controls on every measure ($p < 0.001$, binomial test). Trends ($0.01 < p \leq 0.10$) were evident for the Wechsler Full Scale and Verbal IQ scores (Verbal IQ mean±[SD]: 104.5±[16] vs 113.6±[13.5]; $p = 0.04$) and for measures of attention, reading comprehension, and vocabulary.

Conclusion: These results provide preliminary evidence of a post-HUS central nervous system deficit, and deserve further investigation in a larger study.

Diagnostic Tests for Febrile Infants Less Than 3 Months of Age: A Scientific Overview

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Purpose: To select diagnostic tests which confidently identify febrile infants ≤ 3 months of age presenting to an outpatient facility who are at low risk for serious bacterial infection (SBI).

Methods: A comprehensive computerized search and bibliographic review of relevant articles. After independent review by two observers, 10 of 333 originally identified titles were selected which addressed the purpose of this overview. Two observers independently assessed studies using explicit methodologic criteria for evaluating the quality of studies dealing with diagnostic tests.

Results of data analysis: The best likelihood ratio was obtained by pooling the results from two studies which: had similar diagnostic tests, did not have significant heterogeneity ($p = 0.32$), and had high methodological validity. This pooled estimate of the negative likelihood ratio (95% CI) for SBI = 0.03 (0-0.23).

Conclusion: Assuming a pre-test probability of 10% for SBI, the post-test probability (95% CI) = 0.3% (0-2.5%).

General Pediatricians as Consultants to Rural Family Physicians: A Strategy to Improve Care for Rural Children with Chronic Conditions

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In rural communities without pediatricians, family physicians (FPs) provide the medical home to children with recurrent or chronic conditions. The scarcity of rural doctors plus the high volume and broad range of their practices, limit the FP's capacity to address fully the special needs of these children. Nebraska's Rural Partnership for Children Healthy Tomorrow's Project has implemented an effective strategy to increase access to comprehensive pediatric care, strengthen the quality of care, and improve coordination of services for rural children with chronic and recurrent conditions. General pediatricians recruited through the state chapter of the AAP serve as consultants in monthly clinics held in local physicians offices in a remote four county area. Consulting pediatricians share state-of-the-art information on pediatric topics with the FPs. A locally-based nursing-child advocacy team provides care coordination and follow-up. In the first project year, 67% of FPs in the area have referred children for consultation. Principal reasons for referral: growth and development concerns (35%), behavior and learning disabilities (22%), recurrent infections (15%), and asthma/allergies (12%). The 93% kept-appointment rate of the pediatric consultation clinic is comparable to that of local providers (92%). Through this partnership, geographically isolated children and their families now can benefit from pediatric consultation in their own medical home.

Private Practice Perspective in Suspected Child Sexual Abuse

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This study assesses Central New York (CNY) private practitioners' (MDs) awareness, management and referral patterns of suspected child sexual abuse (SSA). Of 218/339 (64%) family practitioners and pediatricians who returned surveys, 40% were pediatricians and 64% were >10 yrs post-residency. During routine exams, many MDs recognized historical (77%), behavioral (57%), or physical signs (85%) of abuse; few asked relevant historical (32%) or behavioral (27%) questions. During their practice careers, 189/215 (88%) MDs reported at least one case of SSA to appropriate services. Forms for documentation of SSA were used by 23% of MDs. In prepubertal children, 73% performed tests for sexually transmitted diseases; 33% utilized chlamydia antigen assays. Despite accessible child abuse registries, 29% had no available hotline numbers in their offices. Male MDs >10 yrs post-residency were more likely to refer SSA patients. If available, 99% of MDs indicated they would utilize medical consultation for SSA. The need for SSA education for CNY MD's is identified.

Measles and Croup

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In a retrospective analysis from July 1, 1990 to June 30, 1991 of 71 patients hospitalized with measles, 23 (32%) had a diagnosis of croup. The mean age of the 23 patients with measles and croup was 16 months, and 15 (65%) were male. Otitis media was present in 11 (48%) patients, pneumonia in 8 (35%), and dehydration in 7 (30%). Six patients (26%) had previously been immunized against measles, 13 (56%) had not, and in 4 (17%) patients this information was not available. Five (22%) patients required intensive care, 4 of whom were admitted directly to the unit, and 1 was transferred from the ward. Seven (30%) patients were given racemic epinephrine aerosols for treatment of upper airway obstruction, and 1 was treated with nasal continuous positive airway pressure. No patient required intubation and there were no deaths. Patients with a respiratory rate greater than 40, a white blood cell count above 10,000 or stridor at rest, were more likely to require intensive care. Fever, gender, age, duration of measles or croup symptoms at the time of presentation to the emergency department, and prior immunization status, were not predictive of the clinical course. We conclude that measles and croup is not uncommon, and is potentially life-threatening. We recommend that all patients with measles and croup be hospitalized for observation and supportive care.

Ventilation of Infants by Emergency Medical Technicians

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Prior to this study, basic-level Emergency Medical Technicians (EMTs) in a large urban system were trained to ventilate adults using mouth-to-mouth (MTM) and bag-valve-mask (BVM) techniques, but were only trained to ventilate infants with MTM. To determine if EMTs require specific training in BVM ventilation for infants, 65 EMTs were randomly selected to be evaluated in their ability to ventilate an infant mannequin using MTM and BVM techniques. A successful ventilation sequence was defined as: extension of the head from a flexed to a neutral position without hyperextension during ventilations; visible chest rise more than 75% of the time (>15/20 ventilations); and the absence of stomach distention (a visibly convex, palpably tense stomach bladder protruding above the plane of the chest wall).

EMTs had a mean (SD) of 8.0 (4.8) years of field experience. 38/65 (58%) failed the ventilation sequence utilizing BVM, 23/65 (35%) failed utilizing MTM (McNemar's test, $p < .01$). The difference in failure rates between BVM and MTM ventilation sequences was due to the difference in stomach distension rates (BVM 45%, MTM 15%, $p < .001$). There was no significant difference between BVM and MTM with respect to rates of appropriate airway opening or achievement of visible chest rise. A successful ventilation sequence utilizing either BVM or MTM was not related to years of EMT experience (power = 0.8 to detect a 2.7 year difference in experience).

We conclude that adult BVM training and extensive field experience as an EMT are not adequate to ensure effective BVM ventilation of infants. EMTs must be specifically trained in BVM as well as MTM techniques for infants.

Teaching Developmental Milestones to Residents Through Use of Screening Tests

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Teaching aspects of normal child development to pediatric residents often occurs in a somewhat haphazard and incomplete fashion. A study was done to to determine whether residents can learn about normal developmental milestones by learning and performing standard developmental screening tests. A total of seventeen pediatric residents participated in this study during the first six months of each resident's PL-2 year. Each resident filled out a five item questionnaire to collect data about prior knowledge of child development. A pre-test of 20 multiple-choice questions was given prior to instruction and practice of a standard developmental screening test. These were followed by a post-test. Analysis of the resultant data found that 12 residents had some prior use of screening tests and most felt "somewhat" knowledgeable about development (prior to the instruction). The mean pre-test and post-test scores were, respectively, 13.24 (range 11-16) and 18.06 (range 15-20). This improvement was statistically significant ($p<0.001$) using Wilcoxon rank-sum test. The results of this study appear to indicate that residents can learn about developmental milestones while they are also learning how to perform developmental screening tests.

Impact of Neonatal Circumcision With Local Anesthesia on Brainstem Auditory Responses

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Dorsal penile nerve block (DPNB) for anesthesia during neonatal circumcision has been shown to decrease the pain and stress of the procedure. Its use has been limited by concerns about the safety of DPNB, including possible effects of lidocaine on the neonate's brainstem auditory evoked response (BAER) cited in the report of the American Academy of Pediatrics Task Force on Circumcision. This study was undertaken to assess the impact of circumcision with DPNB on the neonatal BAER.

Ten healthy, non-jaundiced, full-term infants whose parents requested circumcision were studied. BAER's were performed by a certified audiologist before and one hour after circumcision with DPNB. BAER's before and after circumcision were compared using the paired t-test.

All BAER's were within accepted normal limits, before and after circumcision. Waves I, III, and V, interpeak latencies I-III, III-V, and I-V at 60 dB and wave V at 30 dB measured before and after circumcision were all highly correlated (p values < .05). The mean lidocaine level was 17.9 ± .52 nmol/L measured 60.0 ± 3.85 minutes after anesthetic injection.

These data demonstrate that a normal BAER prior to circumcision continues to be normal after circumcision with DPNB. Decisions on the use of DPNB for neonatal circumcision should not be based on concerns about the effects of lidocaine anesthesia on neonatal hearing.

A Retrospective Review of Acute Visits With the Diagnosis of Anaphylaxis in Children Over an Eleven Year Period

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Anaphylaxis is an uncommon but potentially life-threatening condition in children. To determine the frequency with which appropriate followup care and patient education was provided, we reviewed the records of the 37 patients under 18 diagnosed with anaphylaxis, who presented to our acute care facilities from 1980 to 1990.

The number of cases per year ranged from 1 to 8. Seasonal variation was small. The age distribution of the cases was fairly uniform. Males represented 62% of the cases. 38% of the cases had a history of atopy. The cause was presumed to be IgE-mediated in 48% of the cases, exercise-induced in 3%, contrast media related in 3%, and unknown in 46%. Presenting signs and symptoms involved the skin in 97% of the cases, lower airway in 62%, upper airway in 43%, nose in 19%, GI in 11%, eyes in 5%, and cardivascular system in 3%. Epinephrine, H1 blockers, and steriods were used singly or in combination for treatment. 51% of the patients received epinephrine and an H1 blocker, 11% required no treatment, and 8% were hospitalized.

Documentation of being prescribed injectable adrenalin for home use was found in 62% of the cases. Overall, appointments for followup were documented in 76% of the cases with 71% of these appointments kept. In the 15-18 age group, appointments were made in only 45% of the cases, but 100% of these appointments were kept. However, in the 5-14 age group, appointments were made in 94% of the cases but of these only 56% were kept.

The management of anaphylaxis involves recognition, medical treatment, and education about both prevention and anticipitory preparation. This study shows that we need greater emphasis on the importance of followup for education especially in the 5 to 14 year age group.

Genitourinary Tract Findings in Cocaine-Exposed Infants

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Cocaine use by pregnant females has been associated with teratogenic effects in experimental animals and has been linked to an increased risk of genitourinary tract anomalies in humans. In the general population the incidence of significant urinary tract abnormalities in healthy infants has been reported to be 1.4%. The purpose of this study was to determine the frequency and pattern of genitourinary tract abnormalities in cocaine-exposed infants. Using renal ultrasound, we conducted a prospective study.

Of 158 infants, 150 had normal renal ultrasounds. Six had mild pelvic dilation (all less than 1 cm). One female infant with mild masculinization of the external genitalia had a normal ultrasound. One infant with hypospadius and a 2 vessel cord had an obstructive anomaly. On routine prenatal ultrasonography, one child was thought to have a hypoplastic right kidney. Postnatal evaluation revealed an ectopic right kidney with normal renal function.

In conclusion, no infant studied solely on the basis of cocaine exposure had a significant urinary tract anomaly on renal ultrasound. The incidence of uropathology appears to be comparable to that reported in the general population.

Duration of Clinical Response to Racemic Epinephrine in Children With Croup

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The objective of this study was to better describe the clinical effects of nebulized racemic epinephrine (RE) in the treatment of croup and to characterize the often referred to "rebound phenomenon". In the emergency department, patients with the clinical diagnosis of croup were evaluated by the principle investigator (PI) using a Fogel croup score. Patients were eligible if the initial score was greater than or equal to 4 (equivalent to stridor at rest and moderate retractions) after a normal saline nebulization. 23 patients between the ages of 3-25 months were enrolled, with a mean initial croup score of 4.091±.197. Patients then received RE 0.5cc in 3cc normal saline and were scored by the PI at 1/2, 1, 2, 3, and 4 hours after the RE. All children were admitted. Change in croup score at various times after the RE:

This data indicates that the usual duration of RE's clinical effect in children with moderately severe croup is 1-2 hours. No significant clinical worsening compared to initial status (i.e. rebound) was noted.

The Communication Screening System: Preliminary Hearing Validation

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The overall goal of this project is to develop an efficient means to simultaneously screen for speech, language and hearing problems in pediatric practice. The objective of this study was to make it possible to use speech stimuli for screening by overcoming known obstacles, e.g., insensitivity to conductive hearing loss. Items were selected through a series of studies to establish: (1) the potential of a sentence repetition paradigm for speech and language screening; (2) the vocabulary level of words potentially sensitive to hearing loss; (3) the performance/intensity curves of speech stimuli (with and without maskers) to define the point just prior to when normal subjects begin to deteriorate in performance. The resulting speech stimuli with background babble noise were presented via interactive computer to 51 children (aged 3-5) who also received diagnostic speech, language, and hearing testing and tympanometry. Discriminant analysis of children with (N=17) and without (N=34) middle ear dysfunction resulted in a sensitivity of .94, specificity of .88 and predictive value of .94.

White Blood Cells on Wet Mount

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Patients' symptoms are of limited use in the diagnosis of sexually transmitted diseases (STD's) and cultures have significant false negative rates. Another indicator was sought to aid such diagnoses. WBC's were observed on wet mounts to see if increased numbers correlated with STD's particularly gonorrhea and/or chlamydia. A method was also developed for quantitating numbers of WBC's on wet mount. 401 adolescent women were evaluated including a history, pelvic exam, wet mount, and cultures. 250 patients had WBC's present on their wet mounts. These were divided into groups according to the number of WBC's present. Quantitation was established by comparing numbers of WBC's to epithelial cells/hpf. This was found to be more accurate than previous quantitation methods which counted numbers of WBC's/hpf. Group 0 (no WBC's) had a 10% positivity rate of gonorrhea or chlamydia cultures. Group 1 (WBC's < epithelial cells) had a positive culture rate of 15%. Group 2 (WBC's +

pithelial cells had a 23% culture positivity. Group 3 (WBC's > ep-helial cells) had a 37% culture positivity rate. Excluded from these revious groups were patients with documented trichomonas. Tri-homonas is detectable on wet mounts in only 50% of culture positive ses, therefore, it can be assumed trichomonas accounted for some f the WBC's in Groups 1-2. Excessive WBC's on wet mounts seem be a reliable indicator of STD's (trichomonas, gonorrhea, or hlamydia) and may assist in making a diagnosis where other clinical b indicators are lacking.

nfant Walker Use In Private Practice Populations

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Infant walkers have recently received attention as a potential cause f injury to children. We undertook this study to determine the extent f use of walkers in private practice populations and the potential risk f injury to that population. Questionnaires were completed by parnts of 234 one year old children followed in seven pediatric practices. Ninety-two percent (92%) reported having used walkers with their nfants. By four months of age 41% had begun use; 99% had stopped se by one year of age. Twelve percent (12%) reported their child receiving an injury while in the walker, the most common type being minor head injury (36% of those injured). Fourteen percent of older hildren in the family were reported to have sustained injuries in walkers. The incidence of walker use and injury occurring during use s worthy of further attention. Patterns of use suggest early anticipatory guidance may decrease both use and injuries.

he Knowledge and Attitudes of School Nurses Regarding Stimulants or Students With Attention Deficit Hyperactivity Disorder

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Increasing numbers of students are receiving stimulants for Attention Deficit Hyperactivity Disorder (ADHD). School nurses may be esponsible evaluating students for side effects. We wished to assess he knowledge and attitudes of school nurses about stimulants.

Two hundred and twenty one school nurses attending a statewide onference completed a questionnaire regarding stimulants. Nurses enerally felt that stimulants were useful. Most of the nurses had received little training about stimulants, yet 86% of them felt that stimulants were one of the best treatments for ADHD. Over 75% were ware that stimulants might cause headaches or stomachaches; most were aware that stimulants could improve concentration and decrease impulsiveness. Only half of them were aware that tics might e associated with stimulants.

School nurses are well informed about stimulants and should participate in monitoring students on stimulants.

actors Associated With Acuity of Visits in Preschool Age Emergency Department (ED) Patients

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Objective- To examine factors associated with acuity of visits among preschool age ED patients.

Design- Cross-sectional survey. Guardians of ED patients were asked about their child's socioeconomic status, health status, health nsurance, source and use of primary care, and reason for the ED visit. We rated visit acuity as high, medium, or low on the basis of admission, performance of tests, and ED MD subjective evaluation.

Setting- A pediatric ED in an urban teaching hospital in Rochester, NY.

Subjects- 605 children, ages 4 to 48 months, who were residents of Monroe Co. were consecutively enrolled.

Results- Subjects had the following characteristics: 55% white, 42% black; 10% of Hispanic origin; 60% male. 50% had Medicaid and 5% were uninsured; 16% had no telephone. Subjects reported that they received primary health care at a teaching hospital clinic (28%), neighborhood health center (22%), private MD (50%), or had no MD (<1%). 56% reported having been referred in by their MD. Chronic health problems were noted in 25% and these patients tended to have made more frequent ED visits (p<.001). Acuity of visit was higher for patients who registered during day shift, attended a private clinic, had private insurance, were referred in by their primary MD, had no previous ED visit, and assumed their cost for the visit was > S0 (p= .001, <.001, <.001, <.001, and <.001, and .015, respectively). Chronic health problems and arrival by ambulance were **not** associated with higher acuity.

Implications- Access to primary care during evenings and nights, awareness of MD availability by telephone, and cost-sharing may reduce low acuity ED visits.

Psychosocial Factors in Adherence in Asthma Medication Regimens

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With the recent rise in asthma morbidity among urban children, medication adherence has become an increasingly important issue for health care providers. However, little is known about the role of psychosocial factors in adherence. The current investigation examines the association between medication adherence, as assessed by the question "Do you have difficulty getting your child to take his/her medications," and several dimensions of family and individual psychological functioning. Fifty four families of black children aged 5 1/2 to 12 with moderate to severe asthma completed an extensive interview pertaining to asthma symptoms and management practices as well as self-report measures of child behavior and adaptation, family environment, and parent psychological symptoms. One third of the sample reported difficulty getting their child to take his or her asthma medications. Difficulties with adherence were associated with greater behavior problems in the child, higher levels of family conflict, and lower levels of family organization. Moreover, nonadherent children experienced significantly more hospitalizations during the previous year. These preliminary findings suggest that psychosocial factors may be important determinants of adherence to asthma medication regimens.

Persistence of Cultural and Language Bias in the Testing of African-American and Latino Preschool Children

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Inner city minority children are faced with numerous barriers that impact on their developmental functioning. It is crucial that developmental concerns be identified and remediated early and be carried out in a culturally sensitive fashion. Within the context of a community-based, preschool intervention program housed at a neighborhood health center serving predominantly low income Latino and African-American patients, participants (N = 79) were administered cognitive and achievement measurements. In order to optimize the performance for non-English speaking children, the **James T. Language Dominance Test** was administered to children who were from bilingual homes to determine their language dominance and testing was conducted in the child's dominant language. All children were administered the **Kaufman Assessment Battery for Children** (K-ABC), which is considered to be a fair measure for minority children. Spanish dominant children (N=31) uniformly exhibited lower scores than English dominant children (N=48) on the major sections of the K-ABC including: Mental Processing Composite (I.Q.), math and reading achievement. There was an 8 point discrepancy in I.Q. scores (p = .006), a 4 point difference in math (p = .14) and a 9 point difference in reading (p = .02). When these findings were examined in covariance analysis which controlled for the effects of poverty, chronic illness, family disruption, maternal education and age at first pregnancy, the effects of Spanish dominance remained marginally significant (p = .06) on the MPC (I.Q. score), but were non-significant on math and reading achievement. Test bias is a topic of frequent debate and discussion in the testing of bilingual and minority children. Our findings support that more sensitive and thoughtful methods of intellectual assessment are required to meet the needs of bilingual minority children.

The Microbiology of Middle Ear Aspirates from Children With Acute Otitis Media Seen in Denver, Colorado

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Tympanocentesis was performed on 109 children. Overall a pathogen was isolated in 79% of middle ear aspirates (MEA's); 68% had a single pathogen and 11% multiple pathogens. Non pathogens were isolated in 9% of MEA's, and no bacteria were isolated in 12%. S. pneumoniae and H. influenzae were isolated in 42% and 41% of the MEA's with pathogens. Other pathogens were M. catarrhalis (9%), S. aureus (4%), S. pyogenes (2%), enterococcus (1%) and Group B streptococcus (1%). The overall proportion of pathogens that were beta lactamase producers was 26%. All M. catarrhalis and S. aureus organisms and 31% of H. influenzae organisms produced beta lactamase. The proportion of pathogens resistant to TMP/SMZ was 6% (S. pyogenes, Group B streptococcus and enterococcus). Among 27 H. influenzae and 28 S. pneumoniae organisms with MIC performed, one of each organism had an MIC $>$4/76 against TMP/SMZ. All pathogens isolated were susceptible to either TMP/SMZ or amoxicillin.

Total IgG and IgG Subclass Levels in Children With and Without Recurrent Otitis Media

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Total IgG and subclasses IgG1, IgG2, IgG3 and IgG4 were measured in 89 subjects with recurrent otitis media and 30 controls. There was no significant difference between the groups with respect to the arithmetic or geometric mean levels for total IgG or any subclass. Two of 30 (6%) control subjects had an IgG subclass deficiency; 1 with IgG1 and 1 with IgG3. Nine of 89 (10%) recurrent otitis media subjects had an IgG subclass deficiency; 2 with IgG1, 6 with IgG3 and 1 with IgG4. No IgG2 deficiencies were noted in either group. There was no significant difference between total IgG or subclass levels of controls and recurrent otitis subjects who, on prophylaxis, had no new otitis episodes, one episode, or two episodes. Determining total IgG and subclass levels has limited clinical usefulness in predicting who will develop recurrent otitis media; or who will need ventilating tubes.

Factors Effecting Outcome of Children Treated With Antibiotics for Acute Otitis Media

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The interpretation of antibiotic trials for acute otitis media requires an adjustment for confounding factors that effect outcome. The proportion of children cured or improved at the 3 week post therapy visit was lower for children with ≥ 3 prior otitis episodes (17/46) compared with <3 prior otitis episodes (37/56) ($p=0.003$), for children enrolled during the winter months (30/68) compared to non winter months (24/34) ($p=0.012$), and for children who had received antibiotics in the month prior to entry (14/40) compared to those who did not receive prior antibiotics (23/42) ($p=0.072$). Children treated in the trial with cefaclor had a lower cure or improved rate (8/25) compared to children treated with cefixime (20/38), Loracarbef (8/14), Augmentin (9/16) or Amoxicillin (9/9) ($p=0.014$). Only prior otitis media episodes ($p=0.003$) and season of enrollment ($p=0.011$) met the 0.05 significance level for entry into the model derived from logistic regression to assess interactions among the factors.

How Do Children With Medicaid Use Their Pediatrician for Sick Care?

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There is a perception among health care providers that Medicaid patients over-utilize health care. Do children with Medicaid use their Pediatrician for more sick care than other children?

We analyzed 8.5 years (1982-1990) of patient visit data from an academic pediatric continuity clinic at the Medical University of South Carolina, 42,267 sick visits (25% Medicaid) by 5,289 patients. Analysis was by ANOVA controlling for the age of the patient.

The average number of visits by a patient by age category was:

Age (yrs):	0-2	3-5	6-8	9-11	12-14	15-17
MOP: Medicaid:	5.13	4.05	4.05	4.11	5.54	6.68
MOP: Other	4.47	3.07	2.92	2.75	2.52	2.55

Method of payment (MOP, Medicaid vs other) and the interaction between insurance and the above age categories (AGE) were significant predicators of number of clinic visits (MOP and MOP*AGE, $p<0.0001$).

Further analysis addressing the effects of acuity and chronicity are in progress. However, the present analysis support the common perception that Medicaid patients utilize more medical care.

Child Abuse and Neglect: The Status of the State Statutes

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To assess the feasibility of a coordinated national effort in response to alleged child abuse and neglect, we analyzed the 50 separate state statutes. The provisions for central registries and investigations of allegations were reviewed, including how law enforcement (LE) and social service (SS) investigations are coordinated. Forty-two states have central registries; only 5 states stipulate that their registries may be used nationwide. Purposes of the registries range from tracking potential perpetrators to monitoring statistics and planning for services. In 13 states investigations are carried out by either LE or SS. The remaining states mandate SS investigation only, and have diverse provisions for if and when LE should be involved. Our data suggest that the multiplicity of separate state statutes produces inconsistency in evaluation and data collection and might contribute to the current lack of a national data collection system. More uniform procedures and state central registries would be useful steps toward a more coordinated national system.

Video as an Educational Intervention for Childhood Asthma Among Urban Blacks

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We have shown previously that participation in a 1-day asthma camp curriculum, using a collaborative multidisciplinary team approach between Univ. & community-based staff provides an effective educational intervention for childhood asthma among 5-10 yr old urban blacks (UB). Based on our prior data, we hypothesized that an asthma self-management video using our multidisciplinary approach with pre/post viewing questionnaires for assessment would provide an effective low-cost high-impact educational intervention for UB. Video content was assessed by a literacy team & included: signs, symptoms & triggers of asthma; aerosol, inhaler & peak flow meter use; normalizing child's physical/social activities & guidance for intervention with health care providers. Pre/post questionnaires measured: knowledge, behavior & attitudes about asthma. Video/questionnaires were given to 34 participants (X age=8.0 yrs; black 91%; male 70%) at asthma camp. Questionnaire percentile scores revealed:

	Pre	Post	P Value
Knowledge	82.8%	93.8%	<0.001
Behavior	78.3%	95.2%	<0.0001
Attitude	71.0%	95.2%	<0.001

Overall, participation was associated with 16%-25% improvement in knowledge, behavior & attitude scores on childhood asthma. A randomized trial is planned to further examine the effectiveness of this educational low-cost high-impact intervention in this population.

Pediatric Dental Emergencies

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We prospectively studied diagnosis, management, and follow-up of dental emergencies in an urban pediatric ED. Of the 104 patients enrolled, 92 had dental trauma. The most common injuries included tooth fracture (26%), subluxation (22%), gingival laceration (22%), avulsion (22%), intrusion (10%) and extrusion (10%). Of the 24 patients with tooth fractures, 33% had pulp exposure. 17 of the 19 patients with avulsions brought the tooth to the ED, with a median elapsed time from injury of two hours. The most commonly injured teeth were the central incisors (86%), followed by the lateral incisors (26%). 70% of the dental injuries occurred in the home; most were falls (69%). Among non-traumatic dental emergencies, dental caries (41%), and tooth pain (16%) were most common. The most common treatments in the ED were extraction (13%) and splinting (7%). We obtained dental follow-up information on 44 (42%) patients. For these patients, the ED diagnosis was felt to be correct 91% of the time, and the treatment correct in 89% of cases. Dental emergencies are commonly seen in a pediatric ED. Physicians caring for these patients must be aware of the principles of dental emergency care.

Cervical Spine Immobilization: Time for a Change

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Immobilization of the cervical spine(CS) is vital in the emergency management of multiple trauma. Extension of the CS is preferred during immobilization and transport for preventing further injury. However, current methods for immobilizing young children may actually force the CS into dangerous flexion. This study was performed to determine whether children <7 years of age with and without semi-rigid cervical collars have flexed cervical spines.

Twelve children <7 years of age presenting to our ER requiring CS x-rays had lateral films with and without a semi-rigid collar. All children were taped and secured to back board. C2-C6 lateral cobb angles were measured on both lateral films. Mean flexion with collar was 5.8 degrees and 6.3 degrees without a collar $p > 0.05$.

Our study found that children less than 7 years of age when immobilized on back boards are placed into a dangerous degree of CS flexion. Application of a semi-rigid cervical collar does not improve flexion. Further study is needed to develop and test safer methods of CS immobilization as present equipment is unable to position the CS correctly.

Earrings: A Piercing Question

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Ear piercing (EP) is one of the most common surgical procedures performed in children. Yet little data are available on the complications(CMPS) following it or the relationship between CMPS and age, race, or other variables. This study attempted to determine the prevalence and types of CMPS after EP and the variables associated with them.

Self administered questionnaires were given to parents of females <12 years of age ($n=1717$) presenting to 6 clinics in the Detroit area. Fifty two percent had EP, with 31% reporting CMPS. Most CMPS were consistent with nickel dermatitis: 91% having either rash, drainage, crusting, or redness not requiring antibiotics. Keloids (3%) and embedded (2%) earrings were also reported. Ten percent visited a pediatrician to treat CMPS. CMPS were fewer in infants $p<.0001$, black children $p<.001$, and with use of gold earrings $p<.05$. Site of piercing, piercing method, and care of the pierced ear were not associated with complication rate.

Our study found that CMPS following piercing are common; most secondary to nickel dermatitis. Infants, blacks, and those not using nickel containing earrings had fewer CMPS. Avoidance of nickel containing earrings would substantially lower complication rates in children with pierced ears.

Early Biopsychosocial Indicators of the Vulnerable Child Syndrome (VCS) in Preterm Infants

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Preterm infants may develop VCS, but many of them do well and are seen as normal by their parents. We hypothesized that preterm infants whose mothers had low social support or high depression scores would be more likely to develop VCS.

Before NICU discharge, we assessed risk factors in 27 prematures by the Neurobiologic Risk Score, the Maternal Social Support Index (MSSI), and the Center for Epidemiologic Studies Depression Scale (CES-D). Six weeks later we evaluated health care use, separation and feeding patterns.

All mothers with previous pregnancy loss and 57% of mothers with low community involvement (MSSI7) sought urgent care for their infant. Over 80% of mothers of twins had high depression (CES-D) scores compared with 17% of mothers of singletons ($p<.05$). A persistently high CES-D score at follow up was associated with feeding changes ($p=.10$).

Biologic risk was not associated with early signs of VCS among preterm NICU survivors. Interventions for mothers with previous pregnancy loss, low social support, or prolonged depression may prevent VCS in preterm infants.

Impact of an Algorithm for Preschool Immunization Opportunities

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Immunization rates are low in preschool children, especially among children in low income families. A recent study in our hospital-based primary care center(PCC) serving lower socioeconomic status families in Rochester, NY revealed that 82% of children missed at least one opportunity for immunization (IZ) over their first three years of life and IZ were rarely given at non-well child visits. The majority (64%) of the missed opportunities occurred at acute illness visits, 11.3% at WIC evaluation and administrative visits and 12% at follow-up visits for acute problems. In response to these findings, an algorithm was developed to serve as a standing order for nurses to evaluate IZ opportunities and administer IZ's at all non-well child visits. This algorithm was incorporated into an IZ opportunity assessment form (IOF).

732 IOF's were completed for children aged 2-60 months during a 5 month period in 1991. As determined by the nurses using the IOF, 98 (13.4%) visits had one or more IZ lacking. Of 139 IZ due at these visits, 91 (65.5%) were given. 74.2% of the IOF's were completed for children at acute illness visits, 19.9% at WIC visits, and 5.9% at administrative visits. In the absence of fever, most IZ opportunities were used and the proportion varied little by vaccine (87% for DTP, 88% for OPV, 91% for MMR, and 78% for Hib). In the presence of fever, IZ opportunities were used less often (8.3% for DTP, 37.5% for OPV, 25% for MMR, and 16.6% for Hib) despite the protocol that would suggest it was acceptable in many cases.

The IOF was associated with use of a substantial proportion of IZ opportunities, none of which would have been used in our prior practice.

Pediatric Residents' Continuity Care Clinics: What Are We Really Doing?

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How are we educating our pediatric residents in ambulatory medicine in our Residency Review Committee mandated Continuity Care Clinics (CCC)? As patient care increasingly moves to the ambulatory setting, it is crucial that we develop effective strategies for teaching primary care pediatrics. CCC directors of 158 U.S. pediatric residency programs responded to a survey requesting detailed descriptions of their clinics. Examples of areas assessed included program demographics; the clinic setting and resources; staffing; and resident education, evaluation and scheduling. Results suggest several priority issues including a need for chairman and departmental support of the clinic, curriculum development and enhanced continuity of care for the enrolled patients. The identification of factors which may influence the quality of this experience should help direct development of strategies in curricula design and prioritization of goals.

Gender Differences Among Incarcerated Adolescents on STD Related Attitudes and Behaviors

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This study examined gender differences in STD related attitudes and behavior. A questionnaire was completed by 388 incarcerated adolescents. Attitudes, perceived barriers to care, intentions to change sexual behavior and self-reports of sexual behavior and drug usage were assessed. The median age was 16 and 79% of the participants were male. Both males 82% and females 64% were predominantly black. More males reported weekly sexual activity compared to females (males 41%/females 21%, $p=.002$). 57% of females reported fewer than two sexual partners in the past four months versus 11% for males, $p=.0001$. Males were more likely to use alcohol before sex (male 48%/female 29%, $p=.009$). Males used alcohol and marijuana more frequently (13+ times a year) than females (alcohol: males 47%/females 23%, $p=.0004$; marijuana: males 33%/females 12%, $p=.001$). Females intended to reduce their number of sexual partners more than males (females 75%/males 44%, $p=.0001$) and to abstain from using alcohol or drugs in situations that might lead to sex (female 69%/males 50%, $p=.002$). Females felt it was not OK to have sex with casual acquaintances (female 85%/males 50%, $p=.0001$). Different educational approaches may be needed for each gender when modifying risk for STD's.

Hepatitis B Vaccine: Knowledge, Perceptions and Acceptance Among Health Care Workers in a Major Pediatric Hospital

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Hepatitis B infection among health care workers continues to be a major occupational hazard with reports of 12,000 cases and 250 deaths annually among health care workers. According to previous studies only 40% of American physicians have been vaccinated against Hepatitis B. We employed a questionnaire to survey 800 health care workers in a major pediatric hospital regarding their knowledge, perceptions and acceptance of Hepatitis B vaccine. The questionnaire was completed by 523 employees (65% response). Of these, 382 employees (73%) had been vaccinated and 30% of the employees in this group reported a significant exposure. Among those who had not been vaccinated 9% reported a significant exposure. In the vaccinated group, 36% had their immune status verified after completing a series of three vaccinations. Reasons cited for not being vaccinated were the fear of acquiring AIDS, pregnancy, and fear of side effects of the vaccine. Some felt that they were at low risk for acquiring Hepatitis B. Our data allow us to conclude that our hospital has been very successful in encouraging high rates of immunization partly due to aggressive efforts by the Employee Health Department to vaccinate employees free of charge. However, further study is necessary to determine the current levels of protection in employees and the possible negative effect of previous vaccination on the perception and reporting of significant exposures in those potentially at risk.

Professional Liability in the Emergency Room Setting in a Major Pediatric Hospital

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Risks of malpractice claims tend to be high in a pediatric Emergency Room (ER) both because of the medical acuity of cases seen and because of high parental expectations. This retrospective study defines the nature and pathogenesis of all cases of threatened or actual malpractice claims originating from the emergency room at the Children's Hospital and Medical Center in Seattle. Eight cases were identified over the period 1974 to 1991, with an incidence rate of 4/100,000 visits. Appendicitis, meningitis and epiglottitis accounted for 62.5% of the cases.

Factors which may contribute to the low rate of malpractice claims at our hospital may include several structural systems that have been implemented to enhance the quality of care rendered. One such system is the use of ER staffing 24 hours a day 7 days per week by an ER attending physician, made possible by use of a night float system. A very intense quality assurance program, the use of standards for response time for consulting services, and availability of an epiglottitis team are additional systems which improve quality of care and help lower the risk of malpractice claims.

Examination of the Genitalia of Prepubertal Children by Pediatric Residents

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Prepubertal genital exam (PGE) is an important aspect of health maintenance visits (HMC). There is little information regarding the training of pediatric residents (PR) in performing the PGE. The purpose of this study was to find out from PR how they perform the PGE.

A questionnaire was completed by 149 residents from 7 pediatric residency training programs in Ohio. During routine HMW genital exam was performed in 65% of the girls and in 75% of the boys. Exam of the anus was done in 29% of the girls and in 27% of the boys. Hymenal size was noted in 11%. Seventy percent of the PR explained to the children that they were going to check their genitalia. Ten percent of the PR asked whether they knew what a "bad touch" was. Twenty-one percent of the PR asked if the children knew what to do if someone used a "bad touch" with them. Seventy-nine percent of the PR felt confident performing the PGE of normal children, and 29% felt confident examining sexually abused children. PR felt more confident examining boys whether sexually abused or not. Three percent of the PR missed 4 out of 8 identifying areas on a photograph of the genitalia of a normal 6 year old girl. Fifty-seven percent of PR stated that their most important source of information in performing the PGE was practice during pediatric residency.

Conclusion: pediatric residency training and medical school programs should emphasize teaching PGE.

Peer Screeners to Identify Substance Abuse in Pregnant Teens: A Controlled Trial

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In a previous observational analysis, we found that Peer Screeners (PS) in a Teen Prenatal Clinic were twice as likely to identify alcohol/drug use and equally successful with tobacco use compared to OB practitioners (OBP). This was explored since peer prevention approaches with substance abuse have shown better results than those managed by adults. To clarify the significance of these findings, a controlled trial was carried out in which the OBP were given the same educational materials provided to PS. Patients were randomized to PS (N = 24) or OBP (N = 16), and the same structured questions were asked by PS and OBP. Early results from the controlled trial indicate OBP were more effective than PS in identifying substance use (tobacco 23 vs. 12.5%, alcohol 23 vs. 4%, drugs 25 vs. 0%). Interestingly, PS appear more effective than OBP in elucidating a history of alcohol and drug use by the patient's boyfriends, Relatives Risk 2.7 and 1.6, respectively. Using PS may produce additional useful information in evaluating pregnant teens. A larger controlled trial is needed to clarify and confirm these findings.

Increasing Anticipatory Guidance in Pediatric Care: The Denver Child Health Passport

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Often pediatricians do not devote sufficient time and emphasis during preventive health care visits to the discussion with parents of anticipatory guidance. The Denver Child Health Passport (DHP) is a parent-held complete health record which was designed to actively involve caregivers and parents in the process of health education. It incorporates parental concerns and observations of their child into the caregiver's overall health assessment including screening and developmental delay, immunizations and anticipatory guidance given. Two to four items in the areas of nutrition, injury prevention, developmental promotion and medical/dental education are included for each visit from newborn to six years of age. Health suggestions for parents are printed on durable, tear-off "refrigerator-page" reminders and parents are instructed in their use. The suggestions are written at a third grade reading level to be understood by most families.

A checklist format expedites recording for both provider and parent and facilitates quality assurance and performance feedback.

The DHP is currently undergoing testing through a randomized controlled trial involving half of 300 low socioeconomic families and their newborns. This study will determine the extent the DHP increases adherence by care providers and parents with the American Academy of Pediatrics recommendations for anticipatory guidance.

Method of Payment Influences Mortality Rate in Meningococcemia

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A relationship between lack of insurance and mortality is important but has not been well established. Meningococcemia, a rapidly progressing, critical disease with a high mortality, is an appropriate disease for analysis of this relationship.

Methods: All patients less than 17 years, discharged from hospitals in California in 1986-7, with an ICD-9 diagnosis of meningococcemia (036.2) were stratified by payer group: Private Insurance, Medicaid or Uninsured. Mortality was analyzed by race, age and gender and evaluated by Categorical Analysis of Variance (CATANOVA).

Results: Mortality varied by method of payment, ($p < 0.00001$, $r^2 = 0.02$, N = 269). Uninsured children had significantly higher mortality than insured children, 22.2% vs 7.0% ($p < 0.05$). Age and gender had no influence. Uninsured Blacks had a significantly higher mortality than the study population.

Conclusion: Lack of insurance had a significant influence on mortality in children with meningococcemia. Lack of access for early intervention may be the reason.

Children Missed by the NCEP Pediatric Panel's Recommended Selective Screening Strategy

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The National Cholesterol Education Program (NCEP) Pediatric Panel recommends that cholesterol screening be limited to children with a family history of premature CVD (FH) or parental hypercholesterolemia. We studied 10,457 children (2-19 years) identified by the 1989 Otsego County, NY Health Census (36.6% population sample). Children living in single parent households (N = 1677) were less likely to report known FH than children in 2-parent households (N = 8780): 20.7% vs. 33.6%; most likely reflecting incomplete family health history. 59% of parents reporting not having their cholesterol levels checked. These parents were significantly more likely to have the following characteristics: female sex; single parent; low education level; medicaid recipient; no health insurance; and fewer doctor visits in the past year (all $p<0.01$). Incomplete family health history and undetected parental hypercholesterolemia will seriously undermine the effectiveness of the proposed cholesterol screening strategy. Moreover, it will result in selectively missing hypercholesterolemic chillren from single parent families, families with poorly educated par- nts, and families lacking health insurance.

'ediatric Decision Making: Is It Different in the "Ivory Tower"?

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The majority of pediatric residents are learning to practice medicine n tertiary care university training programs. Most of these same residents will eventually join a private practice. Yet, these residents may be learning a different brand of medicine in these tertiary care centers han exists in the private practice setting. The aim of this study was o determine whether there are differences in common treatment decisions between pediatric residents and private practitioners.

We obtained questionnaires from 107 pediatricians (pediatric residents and private attendings in urban, suburban, and rural settings) elating to general pediatric decision making such as medication usage and acquisition of laboratory and radiologic tests. There were no significant differences in "sick visit" workups where clinical judgment may not be reliable (i.e. fever in less than 4 week olds) and also n acquisition of routine well child laboratory tests (i.e.tympanograms, urinalysis, hematocrits) except where patient population differences were attributable (i.e. screening for sickle cell trait and lead ntoxication). There were, however, significant differences ($p<.05$) between usage of nonprescription and prescription medication for symptomatic relief (topical otic analgesics, antispasmodics, absorptives,antiflatulents, antitussives) and acquisition of radiologic and aboratory tests during most "sick visits" (coin ingestions, pityriasis rosea, simple febrile seizures, fever in 4 to 8 week olds, hyperpyrexia, diarrhea).

Recognizing that many factors may account for these differences (experience, compliance, cost, population differences, etc.), these results suggest, however, that differences in medical practices exist with residents prescribing fewer medicines for symptomatic relief and ordering more tests for most "sick visit" workups than private practitioners.

mproving the Diagnosis of School Problems Using On-Site Consultation

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In place of referral to a tertiary care center, an on-site developmental/behavioral pediatric consultation program was developed in a rural pediatric practice to improve diagnosis and treatment of school problems. All children referred were suspected of having Attention Deficit Hyperactivity Disorder (ADHD). The primary care pediatrician performed a problem-specific history and physical exam. The consultant evaluated the child for learning, attentional, and emotional problems via questionnaires, history and direct assessment. 32 children, ages 6.0 to 13.5, have been evaluated. The diagnosis of ADHD was confirmed in 11/15 previously diagnosed children, and made in 6/17 who were suspected of ADHD. 15/32 children thought to have ADHD did not. 17/32 patients, with and without ADHD, were found to have contributory mental health problems and/or cognitive deficits. The on-site consultant improves diagnostic accuracy at a lower cost, and facilitates linkages with local educational and community mental health resources.

Adolescent Pregnancy Prevention: A Computer-Assisted Intervention

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This study is a systematic block allocation trial of the computer game, BABYGAME, designed to realistically portray the time, money and effort needed for childrearing. Teens 12-19 years attending Harlem Hospital were eligible, completed a questionnaire assessing pregnancy risk, had health care, contraceptive information and workshops available. Pre and posttests and acceptance of the game were assessed.

Participants were 159 teens, 92 in the experimental group, 67 in the control group. Mean age was 15.9 years with 118 females and 38 males. Fifty-four percent had had sex in the past 3 months. Mean age at first intercourse was 14 years and 46% had used no protection. Fifty-four percent had used no protection at last intercourse. Experimental and control groups were comparable. Analysis of covariance with the dependent variables of knowledge and attitude, and pretest as a covariate showed that pretest knowledge of the cost of giving birth to a child and the intervention affected the posttest results ($p<.000$, $r=.685$). Pretest knowledge of the cost to raise a child to 18 years and the intervention affected posttest results ($p<.000$, $r=.543$). The value of protection to avoid pregnancy and whether a child would add problems to a teen's life were affected by pretest attitude and the intervention ($p=.023$, $r=.537$; $p=.010$, $r=.581$, resp.). Ninety-one percent of teens would play the game again. Increased knowledge of parenting demands and the value of delaying parenthood were achieved in this group of teens at risk for early pregnancy. Effect on behavior is being assessed.

The Diagnosis of Child Sexual Abuse

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The diagnosis of child sexual abuse frequently presents a difficult clinical challenge. The objective of this study was to examine the contributory factors to an interdisciplinary team's assessment of 99 children evaluated for suspected abuse. Background information, a history of the alleged abuse, and data from psychological and medical assessments were obtained.

Of the 99 children, 63 were determined to have a moderate-high likelihood of abuse. Of these, 57% had an abnormal physical exam, 49% fully disclosed abuse, and 21% met both criteria. The child's age, characteristics of the alleged abuse, behavior problems on the Child Behavior Checklist, and the child's response to the examination did not significantly contribute to the team's assessment of the likelihood of abuse.

Both a child's disclosure of abuse and an abnormal exam significantly contributed to the team's assessment of abuse. Because a disclosure and an abnormal exam were often not both present, it is critical that all children suspected of sexual abuse receive an individual interview *and* a physical exam.

Developmental Differences in Children With Failure to Thrive

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Developmental differences in cognitive development were examined in 99 low income, inner-city children under 24 month of age with non-organic failure to thrive. Using Maccoby and Martin's classification of parenting behavior, parents were classified into one of four groups (authoritative, authoritarian, indulgent or neglectful) based on the dimensions of warmth and control observed during a feeding interaction. The children's mean developmental score of 94.1 was lower than expected based on normative data ($p<.05$), verifying their high risk status. Using analysis of variance to predict developmental status, a three-way interaction was found between parental warmth, parental control, and children's age ($F = 4.6$, $p<.04$), indicating that parental behaviors associated with developmental outcome differed for infants and toddlers. Infants of parents who were controlling attained higher scores than infants of parents who were neither warm nor controlling ($p < .05$). Toddlers of parents who were warm, yet controlling attained higher developmental scores than toddlers of the other three groups of parents ($p < .05$). Results provide support for the distinction between the dimensions of warmth and control in classifying parents, the need to examine the relationship between parenting behavior and developmental outcome, and the importance of considering developmental differences among high risk children.

Infant Feeding Decisions Among Low Income Women

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Factors that contribute to decisions regarding infant feeding were examined in 64 low income women of full-term infants, half of whom initiated breast feeding in the hospital. All women were receiving Medical Assistance and the groups were matched on maternal age, maternal education, and parity. Most women (89%) made their feeding choice prior to delivery and rated breast feeding as optimal for babies (91% breast feeders and 56% bottle feeders) ($p < .01$). In comparison with bottle feeders, breast feeders reported more support from father and friends ($p<.01$), higher levels of self efficacy ($p<.05$), more advantages of breast feeding for mothers ($p < .01$), and more disadvantages of bottle feeding ($p < .01$). Using a model of behavior change and discriminant function analysis, breast feeding was associated with paternal support and beliefs regarding the advantages of breast feeding for mothers. These findings suggest that breast feeding promotion begin during pregnancy, involve fathers, and emphasize the advantages of breast feeding for mothers, as well as for babies.

Moonlighting Practice by Pediatric Residents

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The purpose of this study is to describe moonlighting practice by pediatric residents, and to determine what factors might influence their decision to moonlight.

Questionnaires were returned from 847 (22%) out of 3,807 randomly selected pediatric residents and fellows in the U.S. Information was sought concerning demographics, educational background, financial situation, level of residency training, career goals, and moonlighting policies and practice. Factors possibly influencing moonlighting behavior were studied to identify their predictive value by linear discriminate analysis.

Moonlighting was practiced by 48.4% of respondents. 73.3% of residents said that their residency directors permitted moonlighting, but only 44.4% of residents said that their residency directors monitored moonlighting practice.

The best predictive factors, when considering all possible factors that determine whether residents moonlight or not, were in descending order: increasing level of residency training, increasing monthly loan payments, decreasing household income, and increasing total medical school debt.

Moonlighting is a common practice among pediatric residents and economic factors are its most important predictors. Since these factors are unlikely to be resolved, residency directors should monitor moonlighting closely in an effort to lessen its potential harmful effects on resident education.

Foreign Bodies and Orifices: Where Do Children Put Things?

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Discharged diagnoses (DD) for Emergency Department visits were retrospectively reviewed for 10 years (1981-1991). Approximately 20,000 visits occur annually, and over 200,000 visits were reviewed. Following DD review, hospital charts on patients with foreign bodies (FB) were obtained. A total of 1008 cases of FB were identified. Patients ranged in age from 2 months to 14 years. There was no significant difference by sex and orifice. Cases of medication ingestion, FB in the skin, and undetermined site for FB totaled 665. Of the FB inserted (N=343), 38% were in the ears, 27% in the nares and 32% were swallowed in the GI tract. Only 2 FB's were found in the vagina and 2 in the rectum. Both vaginal FB's were toilet paper. The rectal FB's were string and a pencil.

Children appear unlikely to place an FB in an unexposed orifice such as the vagina or rectum. FB's, in other orifices, occur not infrequently and pose a risk for injury. Anticipatory guidance against the availability of small objects is recommended.

Outcome of Patients Who Elope From a Pediatric Emergency Department

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It is often presumed that patients who elope from a Pediatric Emergency Department (PED) do not require notable medical care, yet little data exists to support this assumption. We hypothesized that patients who elope (defined as being seen by the triage nurse but leaving prior to physician evaluation) from a PED are at risk for notable illness. To identify and evaluate outcomes of patients who eloped from the Boston City Hospital PED, information was obtained from the PED daily log, triage records, subsequent medical records, and follow-up telephone interviews. Data on demographics, chief complaint, waiting time, reasons for leaving, next health-care contact site, ultimate treatments, and outcomes were recorded. "Notable illness" was defined as any condition which ultimately required an antibiotic or surgical/orthopedic procedure.

Over a ten month period, 142 elopes were identified. Outcome information was available on 101 patients (71%). Data was obtained on 92 (91%) by telephone interview and medical records, and on 9 (9%) by medical records alone. Of the 101, 46 (46%) never sought care for the presenting condition. Of the remainder, 20 (36%) were seen at an office or clinic, 26 (47%) returned to an ED, and 9 (16%) had other means of follow-up. None required hospitalization, 22 (22%) received antibiotics (otitis - 8, sexually transmitted disease - 6, streptococcal pharyngitis - 2, candida dermatitis - 2, others - 4) and 6 (6%) required procedures (lacerations - 3, 1 each for finger/ring entrapment, burn, and gun shot wound).

In summary, 28% of patients met criteria for notable illness; the majority were due to infectious etiologies. Otitis and sexually transmitted disease were common diagnoses.

Depressive Symptoms in School Age Children Entering Foster Care

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Foster children are known to have excessive rates of behavioral and emotional disorders. This study was designed to test the hypothesis that school age children entering foster care have more depressive symptomatology than do non-foster children, and to identify correlates of depression in foster children.

Subjects were 166 children (ages 8-16 years) who entered Baltimore City foster care between 3/90 and 4/91, and stayed in foster care for at least 30 days (mean age 12.1 years, 83% black, and 49% male). The comparison group included 60 students from an inner city Baltimore elementary school (mean age 9.3 years, 100% black, and 48% male). Depression was measured using the Children's Depression Inventory (CDI), a 27-item self report measure of depressive symptoms.

Children entering foster care scored higher on the Children's Depression Inventory (mean score 10.4) than did school children not in foster care (mean score 8.9, $p = 0.04$) or children in the published norms for the CDI (mean score 9.1, $p < 0.02$). Stepwise multiple regression analyses produced no evidence that depressive symptoms in children entering foster care were predicted by age, gender, or race; parental history of affective disorder or substance abuse; history of abuse or neglect; or previous foster care or mental health treatment.

We conclude that school age children entering foster care report more depressive symptomatology than do non-foster children.

Straddle Injuries: A Review

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Urogenital trauma secondary to straddling is commonly seen in the acute care pediatric setting. As urogenital trauma frequently raises the question of sexual abuse, it is important to understand the mechanism of injury in relation to exam findings. This study was done to analyze straddle injuries in relation to demographic and clinical variables.

Cases of straddle injury seen in the Emergency Department over two years were retrospectively reviewed for details of mechanism of injury, demographics, exam findings and therapeutic intervention. 100 cases were reviewed.

Ages ranged from 9 to 187 months (mean 76.4 months); there were 72 female patients. Most injuries were minor lacerations and abrasions of the scrotum or labia. 20 patients were admitted to the hospital for exam under anesthesia or observation. 5 females initially presented with a history of straddling but were subsequently diagnosed as suspected sexual assault (SSA). Hymenal, vaginal and posterior fourchette trauma was found in both SSA and true straddle injury patients.

Ascertaining the consistency between physical findings and history is essential in evaluating straddle injuries as sexual abuse may present initially with a false history.

A Dramatic Increase in Pediatric Firearms Injuries

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A marked increase of the annual incidence of pediatric firearms injuries was recently identified at Children's Mercy Hospital in Kansas City. To identify the epidemiologic trends associated with this increase, a retrospective review of the first versus the last half of the period (1/1/85 - 12/31/89) was undertaken.

A significant increase in pediatric firearms injuries was noted during the latter half of the five year period, yet the demographics of the overall CMH patient census remained the same. This increase was due to an increase in "powder" weapon injuries inflicted by intentional means. Increased median Injury Severity Scores (ISS) accompanied this increased frequency. Pediatric firearms injuries were also significantly increased during the latter half of the five year period in "high crime" areas via census tracts.

Micro-Teaching: A Model for Regional Educational Networking

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Regional networks to share primary care teaching methods and curricula materials could potentially improve education offered to a large group of trainees. However, at present little is known about how to set up such a network and keep it functioning. One APA region reports results of a pilot trial to share micro-teaching sessions (MTS) during the summer of 1991. MTS are brief slide presentations (8-12 slides, 10-15 minutes) on ambulatory topics, suitable for interactive teaching in a variety of busy clinic settings.

Ten MTS created by 3 different centers were distributed to seven programs with instructions to use as many as possible in whatever clinic setting they chose. Five programs completed 57 evaluations. Each session was evaluated at 2-4 centers by 4-8 faculty (average 5.7). Eighty two percent of the sessions were used without modification. Faculty rated 5 variables (topic usefulness, quality of presentation, content, and reception of faculty and learners) with a mean total score of 21 (25 = max).

Participants discussed results and offered suggestions for improvements at their fall regional meeting. They decided to reduce costs and increase participation by trading slide sets (or paper or disk copies) directly with authors. Organizational problems, costs and benefits of this networking system will be discussed, so that other regions may learn from their experience.

Educators' Knowledge and Attitudes Regarding Stimulants in the Treatment of Attention Deficit Hyperactivity

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Stimulants are often prescribed for students with Attention Deficit Hyperactivity Disorder. The effects of stimulants are generally present during the school day; physicians often depend on teachers to look for side effects of stimulants. However, it was out hypothesis that teachers have little knowledge of the side effects of stimulants.

We designed a survey with questions about stimulants and their side effects. The survey was mailed to 311 teachers in two school systems. The overall return rate was 65%. Over 90% of educators indicated that they had received little training about stimulants. Over 30% of teachers had recommended that parents see a physician about stimulants, but over 30% indicated that they knew nothing about the side effects of stimulants. Physicians should work with the educational system to provide more information to teachers about stimulants so they can monitor students receiving them.

Potential Bias in the Evaluation of a Parent Education Program: A Look at Completers vs Drop-Outs

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To assess the extent of "drop-out" bias in a clinic-based parent education program, we compared baseline characteristics of completers and drop-outs in a retrospective case-control study of all parents enrolled from January 1988 to June 1991. Offered at three Seattle pediatric clinics serving low income families, the program consisted of nine weekly sessions taught by an interdisciplinary staff utilizing the Systematic Training for Effective Parenting curriculum. Free transportation, lunch, and childcare were provided for all enrollees. Subjects who attended five of nine classes were classified as completers. Baseline information was obtained from an intake questionnaire, the Adult-Adolescent Parenting Inventory (AAPI), the Nursing Child Assessment Teaching Scale (NCATS), and the Home Observation for Measurement of the Environment (HOME) administered at the session's start. Of the 188 enrollees, 97 (52%) were completers. Completers and drop-outs were similar in ethnicity (43% Caucasian), marital status (70% single), payor status (85% receiving public assistance), high school completion rate (58%), and Child Protective Services referral rate (20%). Baseline AAPI, NCATS, and HOME results were similar in both groups. Drop-outs were more likely to be teenagers (OR 2.81, $p = .0038$) than completers were. Teen parents may be at higher risk for dropping out of parent education programs. Efforts to retain these parents may be necessary to avoid bias in evaluating the effectiveness of such programs.

Routine Admission Hemoglobin Determination: Does it Impact on Patient Care?

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A hemoglobin determination (HB) is essential to management for many children admitted to the hospital, but for others it is done as a required routine laboratory evaluation. We studied 525 children hospitalized over a 4 month period to determine whether routine HBs had an impact on patient care. 510 children had admission HBs; 209 were judged essential to patient management (ESSENTIAL) and 301 were judged not essential to management (ROUTINE). Abnormal HBs (as defined by AAP standards for age) occurred more often in the ESSENTIAL group than the ROUTINE group (42% vs. 23%, $p<0.0001$). In the ROUTINE group, 88% (60 of 68) of the abnormal HBs went unnoted compared to 42% (37 of 88) in the ESSENTIAL group ($p<0.0001$). ROUTINE patients were 10.3 times more likely to have their abnormal HB unnoted than ESSENTIAL patients (95%CI: 4.1-26.9). These data suggest that abnormal HBs were often not appreciated, especially if the HB was not viewed a priori to be essential to patient management. Further investigation is needed to evaluate the consequence of this common oversight.

Screening To Detect a Maternal History of Physical Abuse

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To assess risk factors for dysfunctional parenting, we wished to develop brief screening questions to detect a maternal childhood history of physical abuse. Data were analyzed from a survey of 284 women attending a Family Medicine clinic who completed the 27-item Emotional and Physical Abuse questionnaire. The women had a mean age of 36 years; 88% were white, and 60% had completed college. Overall, 13% considered themselves to have been physically abused as children, 23% reported an intentional injury (e.g. black eyes or broken bones), and 58% reported a potential injury (e.g. having been shaken or choked). Considering self to have been abused had a sensitivity of 56% for detecting actual injury and 22% for detecting potential injury. Actual injury could be detected with a sensitivity of 89% and a specificity of 89% by using four items: self-categorization as abused, history of being shaken, ridiculed in front of others, or being thrown against objects, walls or down stairs. Potential injury could be detected with a sensitivity of 87% and specificity of 94% with 4 items: self-categorization as abused, being shaken, being criticized and made to feel worthless, or being hit with an object. Items dealing with specific injuries were not helpful because of their rarity; items reflecting emotional abuse were highly predictive of physical abuse. As few as four items can reliably detect a history of maternal physical abuse during childhood and can serve as a springboard for further discussion about effective discipline during well child care.

Acquisition of Health Services by Children in Foster Care

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Children placed in foster care are severed from the usual mechanism of accessing health care, namely their parents. In New York City there are over 49,000 children in foster care under the aegis of the Child Welfare Administration(CWA). This represents nearly a threefold increase since 1985. Placements are either into situations directly supervised by CWA or into one of a number of voluntary agencies and can be in kinship or non-kinship foster homes, group homes, therapeutic foster boarding homes or institutionalized care. Previous surveys have indicated the incidence of chronic health problems in foster children to be as high as 50-75% while nearly half suffer from emotional disturbances requiring intervention. The provision of health care services for these children is the responsibility of CWA and the voluntary agencies as their designees. How and to what extent services are provided is largely unknown.

We have designed, with the assistance of the Council of Family and Child Caring Agencies, and distributed to providers of foster care in New York City a questionnaire to assess the following: 1) What medical, dental and psychological services are provided to children in foster care and by whom. 2) How routine and specialty services are administered, coordinated and supervised. 3) What is the immunization status of this population. 4) What barriers exist to the acquisition of comprehensive medical services for children in foster care.

Development of an Outpatient Adolescent Medicine Rotation Based on Use of Community Resources

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Education for pediatric residents in adolescent medicine is an area that has often been neglected. In an effort to incorporate adolescent medicine training into the primary care pediatric curriculum at the Mercy Hospital of Pittsburgh, the program has developed a unique adolescent medicine rotation utilizing community resources.

The rotation has been developed by members of the general pediatric faculty who have a special interest in adolescent medicine. A structured curriculum with specific objectives and associated clinical experiences has been designed and examples include: the identification and treatment of menstrual disorders and the management of common injuries in the teenage athlete.

The adolescent medicine experience utilizes several novel pediatric settings. It focuses on the college health services of two local universities; a Mercy Hospital based adolescent clinic; a public health department sexually transmitted disease clinic; an eating disorders unit of a psychiatric hospital; a community-based family planning clinic; a drug and alcohol treatment center for teenagers and a community based sports medicine clinic.

Since 1989, the rotation has been popular with Mercy's own residents and those of a neighboring pediatric training program. It provides the resident with a broad exposure to adolescent issues and provides an excellent opportunity to administer direct adolescent care.

Future research will be directed at evaluating the adolescent knowledge and skills of pediatrics residents, as well as the impact of the rotation on career selection of medical students.

Effect of Residency Training Experience on Salivary Cortisol Levels

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Residency training may be seen as a paradigm of chronic, recurring stress that can affect performance, psychological and physical health. Cortisol level has been used as a marker of acute stress, but less is known about cortisol response in chronic stress. Measuring salivary (rather than plasma) cortisol levels is a stress-free, noninvasive and reliable assessment of adrenocortical function.

We examined the relationships among self-perceived stress, nature of assigned rotation, and salivary cortisol levels in 26 pediatric residents over 3 sequential rotations. Data was collected at the middle of the first rotation [hypothesized to be a less stressful "baseline"] and the beginning and middle of the next 2 rotations (total of 5 times) and included: hours of sleep, number of on calls, recent illnesses, perception of anxiety and current stress level (using an analog scale), and saliva sample of RIA measurement of cortisol. At times 1 and 5, residents also completed scales measuring stressful events and social support. Preliminary analyses show that salivary cortisol varies with perception of current stress level. As expected, amount of recent sleep appears to influence residents' stress and cortisol levels.

Paramedic Evaluation of Pediatric Advanced Life Support (PALS) on Comfort and Skills Levels During Pediatric Emergencies

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Objective: Obtain a level of paramedic comfort/skill when evaluating or performing a procedure on a child and the effect of PALS certification.

Methods: A voluntary and anonymous survey was presented to all paramedics working at a County's Fire-Rescue departments to gather information of experience, training, exposure to children and PALS certification. Comfort/skill level was asked using a scale 1 = uncomfortable/poor to 5 = very comfortable/superior. "F" test and a two-tailed "t" test of means was used (=0.05).

Results: 441 (56%) completed the survey. 55% of the respondents had attended PALS. Statistically significantly higher level of comfort/skill in the treatment of pediatric trauma and medical emergencies in PALS certified was found. Similar findings were noted during the performance of procedures, respiratory intervention, vascular access, and spinal stabilization in children. Comfort/skill levels were statistically significantly higher in the most experienced with PALS. No differences were observed among the least experienced.

Conclusions: The overall analysis shows that the combination of an experienced paramedic with PALS, is best equipped for pediatric emergencies and a marked improvement in the various activities performed by PALS certified.

Recommendations: Increase the pediatric component in the paramedics curriculum. Consider supplementing the PALS course with regular clinical sessions.

Can Primary Care Referrals in the ED Improve Follow-Up?

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Current emphasis in pediatrics is to decrease inappropriate use of the emergency department (ED) and improve primary care follow-up. A prospective study was conducted at a children's hospital to determine factors that influence a caretaker to bring a child to the ED for a nonemergent problem (NE). After a child was triaged as a NE the family was interviewed, and after medical care, follow-up was arranged with a primary care doctor (PCD). The mean age of the 347 enrollees was 4.4 years, with 51% of the children less than 2 years of age. The children presented with: fever 20%, respiratory symptoms 14.6% and GI complaints 15.4%. The majority of the children (75%) were brought in by their primary caretaker, 50.9% kept their first follow-up appointment. Only 11.7% of the patients brought in by other individuals kept their scheduled appointments. (p<.05) Sixteen percent of the caretakers reported dissatisfaction with their current PCD or they had no PCD. Appointments to a new PCD were kept by 42.9% of these families, while 23% of those with a satisfactory PCD kept their appointment. (p<.05) This type of intervention is most effective with the primary caretaker of a child or a family that is dissatisfied with their PCD.

How Many Children with PB > 10 UG/DL: An answer from Six Years of Venous Lead Screening

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Since October 1985, the General Pediatric Clinic at SUNY HSCB has screened children for lead poisoning with venous blood leads, measured by the NYC Department of Health Laboratories. The proportion of specimens with lead levels above 9 μg/dl (the new CDC case definition) has decreased from an initial 82% in the last three months of 1985 to the range of 20% since Jan. 1990. The decline in prevalence has been accompanied by a decline in the number of specimens with lead levels above 24 μg/dl, which suggests that this trend reflects true decline in lead absorption in our population.

These data are a unique source for estimating the urban prevalence of increased childhood lead absorption according to the new CDC case definition. The new definition poses a threat that the needs of children with unequivocal lead poisoning will be overlooked as already overstressed health departments struggle to deal with the huge numbers of children with now unacceptable lead levels.

Well Child Screening for Behavioral/Emotional Problems

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This study of 41 children (6-12 years old) seen for well child examinations (1) assessed behavioral/emotional problems through a structured clinical interview, the Child Assessment Schedule, conducted separately with children and their mothers; (2) ascertained pediatrician identification of children with behavioral/emotional problems; and (3) evaluated the incremental utility of the mother-completed Missouri Children's Behavior Checklist (MCBC) as a screening measure. Criteria for a DSM-III diagnosis were met by 13 (32%) children by mother-report and 7 (17%) by child self-report. However, only 3 were identified by both reports as having a diagnosis. Of 17 children meeting the criteria for a diagnosis by mother-report and/or child-report, pediatricians identified 5 (29% sensitivity), with a false positive rate of 21% (79% specificity). The MCBC identified 8 (47% sensitivity) with a false positive rate of 12% (88% specificity). These findings indicate that mother and child reports are not interchangeable. Reliance upon mother-report measures to screen for behavioral/emotional problems is inadequate. Child-report measures are also essential.

Developmental Screening by Parental Report: The Child Development Inventories

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This presentation provides information about using parent report—child development inventories for screening young children in ambulatory care. It describes one pediatrician's office research with the Minnesota Prekindergarten Inventory (N = 115 kindergarten eligible children), a briefer Preschool Development Inventory (PDI), for screening 3 - 5 year olds, and the Minnesota Child Development Inventory, for the assessment of 1 - 6 year olds.

Searching for a systematic way to developmentally screen prekindergarten children, the first author began to use the Minnesota Prekindergarten Inventory (MPI) in his pediatric practice. The MPI is a parent report measure of prekindergarten children's *present* development, adjustment, kindergarten readiness, and symptoms. In the practice research, parents MPI reports were compared to: 1) the school's developmental testing (Gesell) and 2) to teachers reports of the child's subsequent performance in kindergarten. Results: The majority of children were normally developing according to parents'

MPI reports (85 percent), while 37 percent were labeled "not ready" by the school developmental testing. Subsequently the large majority of children performed adequately in kindergarten, as would be predicted by the MPI results. Discussion includes how to use parent's child development inventory reports in ambulatory care.

Incidence of Seroconversion To Borrelia Burgdorferi By Immunoblot After A Tick Bite In An Endemic Area For Lyme Disease

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The risk of seroconversion to *B. burgdorferi* following a deer tick (*Ixodes dammini*) bite in an endemic area is unknown, but believed to be small. We evaluated 23 children between the ages of 4 months and 12 years from Long Island, N.Y. after a deer tick bite. Acute and convalescent (>30 days) sera were analyzed for antibody to *B. burgdorferi* by enzyme immunoassay (EIA) and immunoblot (IB). None were treated with antibiotics. One child seroconverted by both EIA and IB. This child had developed a 2-3 cm erythematous macular lesion at the bite site 14 days after the tick bite but disappeared after 2 days before being evaluated by a physician. No other child developed signs or symptoms consistent with Lyme disease. Therefore, 1 of 23 (4%) patients seroconverted following a tick bite. However, 1 of 6 (17%) whose tick was engorged seroconverted. The risk of seroconversion after a deer tick bite in an endemic area appears to be small but may be higher if the tick is engorged.

Loss of Circadian Rhythm in Childhood Essential Hypertension

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The normal circadian rhythm (CR) of blood pressure (BP) is maintained in essential hypertension (EHTN), with lowest readings at night, which increase rapidly in early hours of morning. We studied 5 children with EHTN, using the Space-Lab's oscillometric 24 hour ambulatory BP monitoring (ABM). Their ages ranged from 12 to 21 years with a mean of 15.8 years. The 24 hour mean BP was 130/81 (MAP 90, range 113-152/59-85). The daytime mean BP was 132/75 (MAP 90), and the nighttime mean was 126/70 (MAP 85). We did not find the expected nocturnal fall in BP. Thus, children with EHTN may have a different CR as compared to adults. Since loss of CR is considered a risk factor for target organ damage, these are high risk children and need long term and close follow up. Though the number of patients we studied is not large yet, this attenuated response was seen in every child studied. The use of ABM in pediatric EHTN should be expanded to confirm this observation in longitudinal studies.

Failure of a Prenatal Social Support Program for Indigent Mothers to Influence Their Emergency Cesarean Section Rate

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Background: During the past 20 years this nation's annual cesarean section rate (CSR) has increased from about 5 to 25% of all deliveries. Because a decrease in the CSR has been reported for mothers who receive constant support during labor, we examined 2 subgroups of indigent mothers in two small cities to determine the putative effect of a prenatal social support program (PSSP) on the CSR.

Method: The labor records of 174 mothers were reviewed from this study's two community hospitals. 87 mothers received a PSSP that emphasized enhanced preventive health information, daily problem solving skills and prenatal medical care. They delivered at a hospital with an annual CSR of 25%. A comparison subgroup of 87 mothers, matched for hospital insurance, ethnicity, age and gravidity, was selected from a hospital with an annual CSR of 13% and no PSSP. Data analysis included descriptive statistics, t-test, and multiple logistic regression.

Results: Two thirds of mothers were multiparous, 85% received medicaid and 72% were white. Mothers who received the PSSP were much more likely to deliver by emergency CS (ECS) than mothers who did not receive the PSSP (18.4% vs 2.3%, $p<0.001$). 7 mothers delivered by routine CS and were excluded from the remainder of the analysis. Compared to mothers who delivered vaginally, mothers who delivered by ECS had similar sized newborns (3377+/−41 Gms vs 3468+/−187 Gms, $p=0.6$) and gravidity (2.3+/−.17 vs 2.1+/−.28, $p=0.6$), but longer first stage of labor (433+/−28 min vs 892+/−174 min. $p<0.02$). Using multiple logistic regression, the increased risk of ECS for SSP mothers remained after controlling for six medical (eg duration of labor) and psychosocial (eg maternal education) variables. Relative Risk=2.0 [95%CI 1.6,19.6].

Conclusion: A PSSP may have little influence on the rate of ECS compared to characterisitics of local medical practice including physician training and community patterns of care.

Immunization Status, Health Beliefs, and Access to Care for Urban Hmong Children

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The 1989-90 epidemic of measles in the United States was driven largely by lack of immunization among urban preschool children. In Minnesota, 46% of cases occurred in children of immigrants from Southeast Asia. We reviewed the general immunization status for 204 Asian and 296 non-Asian children attending an urban public clinic, and conducted structured interviews based on the Health Belief Model with 53 Hmong mothers. Immunization records of 162 of the 173 USA-born children of these mothers were analyzed in detail.

At 2 years of age, although more than 88% of all children were up to date for MMR shots, only 51% of Asian children and 68% of non-Asian children were adequately immunized against DPT. In the sample of 162 Hmong children, average delay to immunization increased from a 3.7 month delay for initial infant immunizations to a 15.2 month delay for completing the series appropriate for an 18-month-old child.

Maternal interviews revealed numerous negative beliefs about immunization among Hmong parents (e.g., 73% felt that babies who are small and weak should not have shots). However, parental health belief barrier scores showed only a modest correlation ($p<.05$) with immunization delay at 6 months of age, and no significant correlation overall.

These results, along with the unacceptably low rate of immunization for non-Asian children and further data regarding provider factors, suggest that previously overlooked accessibility problems in addition to health belief barriers must be examined in order to reduce the vulnerability of inner city children to preventable infectious disease.

Is Pediatric Obesity Over-Diagnosed? The Application of Epidemiologic Risk Data to Clinical Settings

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For clinical utility, obesity is most appropriately defined as a condition of excess adipose tissue associated with adverse health outcomes. Limited available longitudinal data show increased adiposity in children and adolescents to be associated with significantly elevated relative risks for current and future morbidity and future obesity. However, relative risks are difficult to interpret in a clinically useful manner. In the clinical setting a "diagnosis" of obesity leads to a recommendation for intervention. As a result, it is more helpful to use sensitivity, specificity and predictive values, the parameters used to assess screening and diagnostic tests. Re-examination of the epidemiologic risk data in this manner yields surprisingly unimpressive crude risks associated with increased adiposity. In addition, the potential risks of over-diagnosis, including labeling, treatment failure, treatment side-effects, weight cycling and economic and non-economic costs, appear to outweigh the potential risks of under-diagnosis, in the setting of relatively ineffective available treatments. Longitudinal data should be used to evaluate characteristics such as age, age of adiposity rebound, persistence of increased adiposity, family adiposity, family morbidity and fat distribution to improve predictive values and identify those patients most likely to benefit from therapy. In the absence of such information, diagnosis of obesity and efforts in weight control should be targeted toward those children and adolescents who currently manifest adiposity-related physical or psychosocial morbidity.

Efficacy of the Lactina Electric Breast Pump (L016) Compared with the Medela Classic Electric Breast Pump (C015)

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The Medela Classic 015 (C015) piston electric breast pump has been used widely to maintain lactation during periods of maternal-infant separation such as infant hospitalization or maternal employment. The smaller Lactina 016 (L016) piston electric pump was introduced in 1988 and was met with enthusiasm due to its lighter weight and increased portability. This study examined the efficacy of the L016 compared with the C015 using 24-hr expressed milk volume as an objective measure of pump performance. Due to the recognized variability of milk yield among women, each subject served as her own control, utilizing a crossover study design. Subjects were post partum women who already were pumping milk for their hospitalized infants using the C015 and universal double collection system. Subjects alternated the use of the C015 and L016 every 24 hrs for a 2-wk study period. Twenty-four women participated in the study, with 80% being enrolled in the first 2 wks postpartum (range 3-40 d). Mean age was 28.2 yrs (range 19-39 yrs), and mean gestation at the time of delivery was 31 wks (range 24-40 wks). No significant differences between the C015 and L016 were observed in the daily number of pumpings, the length of pumping sessions, or total number of minutes subjects pumped each day. Mean 24-hr milk volumes were compared using analysis of variance. While individual milk yields among subjects varied by nearly ten-fold, no significant difference in milk yield was found by pump type. Subjects' mean 24-hr milk yield pumping with the C015 was 540 mls (range 124 to 1156, SD 329.2), and the mean 24-hr milk yield using the L016 was 537 mls (range 120 to 1128, SD 320.9). In this study population, the newer, more portable Lactina 016 was as efficacious as the traditional Classic 015 when comparing pumped milk volumes.

Urban Elementary Students' Understanding of Causality in AIDS, Colds, and Obesity

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Urban elementary students' understanding of causality in AIDS, colds, and obesity was studied in 90 first, third, and fifth graders from two public schools. Ninety percent of the students were African-American and 83% were low-income. A developmentally-based, semi-structured interview (CHILDS-Children's Health and Illness Developmental Survey) was developed to probe children's level of understanding of causality in AIDS, colds, and obesity. Developmental scores ranging from 1 to 6 (least to most sophisticated) were assigned by two independent scorers who were blinded to each child's age, sex, grade, and ethnicity.

An increase in grade level was associated with higher causality scores for AIDS (r = .33, p<.01), colds (r = .44, p<.001), and obesity (r = .22, p<.05). Gender and socioeconomic status were not significantly associated with causality scores. In each grade, mean causality scores were highest for obesity and lowest for AIDS (p<.001 for all).

We conclude that children's conceptual understanding of causality in AIDS, colds, and obesity evolves in a systematic and sequential way with increasing grade level. Within each grade, the finding of lower mean causality scores for AIDS, as compared to scores for colds and obesity, has important implications for AIDS education. Whether children's lack of sophistication about the cause of AIDS results from their limited exposure to AIDS information or reflects some difficulty in their ability to conceptualize this disease needs further investigation.

When Adolescents "Age Out" of Pediatric Health Care Programs: Does Discharge Affect Access to Care?

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For youth chronic illnesses, "aging-out" of pediatric services may lead to diminished access to a regular source of both primary and specialty care. To examine the correlates of age-based discharge, we conducted a cross-sectional study involving 424 persons, aged 19 to 24, who had chronic illnesses. Participants were (1) enrolled in or recently discharged from two programs for Children with Special Health Care Needs (CSHCN) and (2) selected randomly for structured phone interviews. In addition to enrollment status, several demographic and condition-related variables were considered as possible contributors to the absence of a regular source of care for the chronic condition (RSOC/CC) and for general health needs (RSOC/GH). We found (1) proportionately fewer discharged participants had a RSOC/CC in comparison to those enrolled ($\chi^2 = 11.82$; p<.001) and (2) no differences between enrolled and discharged participants in a RSOC/GH. Having a RSOC/CC was also associated with maternal education ($\chi^2 = 8.65$; p = .01), functional severity ($\chi^2 8.18$; p = .02), limits on opportunities ($\chi^2 = 6.96$; p<.01), and receipt of SSI ($\chi^2 = 9.75$; p<.01). Logistic regression confirmed the importance of these variables in predicting presence of RSOC/CC. A very different set of variables comprised the most predictive model for RSOC/GH. Results suggest that discharge from state CSHCN programs negatively affects access to care for chronic conditions.

Yield From Stool Testing of Pediatric Inpatients

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Although stool testing is done noninvasively, it may be ordered indiscriminately for hospitalized patients, generating unnecessary expense. Adults with nosocomial diarrhea almost always have negative stool cultures (SC) and ova and parasite exams (OPE). We hypothesized that too many stool tests are ordered for pediatric inpatients and that we could identify criteria to be more deliberate without sacrificing diagnostic ability.

We reviewed records of all SC, OPE and Clostridia difficile toxin assays (CDA) done on pediatric inpatients, ages 3 days to 18 years, at Thomas Jefferson University Hospital for a 1 year period. Charts were reviewed for positive cases, each with 2 controls matched for age and test.

Of 250 admissions with SC, seven admissions (2.8%) had positive cultures. Of 63 admissions with OPE, one was positive (1.6%). Of 40 admissions with CDA, seven admissions tested positive (17.5%). Only 18/598 (3%) of all tests were positive. Costs of negative tests to patients totaled $26,084 (estimated costs nationally total $14.8 million).

More patients with positive SC than control patients had fever ≥38°C [71% vs 21% (chi-square:p<.05)]; but relying on this sign missed 29% of children with bacterial infection. A blood leukocyte (WBC) band count of ≥10% was 100% sensitive and 79% specific in identifying patients with positive SC. There was no relationship between SC results and age, total WBC or WBC segmented neutrophil count and no relationship between CDA results and all of the above characteristics. C. difficile was the most common pathogen found (6/9) in patients developing GI symptoms after admission; however Salmonella and Shigella were also significant causes (3/9).

In summary, there is low yield from stool testing of pediatric inpatients, especially from OPE. CDA has highest yield and is most valuable for children with nosocomial symptoms. Unlike findings in adult patients, bacterial pathogens can cause nosocomial GI symptoms in children. Although few criteria were found to reduce stool testing, pediatricians might consider limiting stool cultures to children with band counts ≥10%.

Teenagers in Foster Care and Pregnancy Prevention

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The United States has the highest rate of teenage pregnancy among the developed nations. Compared with teens from stable homes, children in foster care have many increased risk factors for pregnancy. Little is known about these adolescents' attitudes toward teen pregnancy.

We administered a questionnaire regarding these issues to teenagers in the Philadelphia foster care system. Preliminary results are based on the first 35 teens in the study. Their average age was 15 years and 57 percent were females. Most (29) were Black and unmarried (34).

Twenty-seven of the 35 teens admitted to being sexually active. Three teens had 2 children of their own and 6 had one child. Ten said they had been pregnant and 3 admitted to having abortions. Nine teens declared they always used some form of birth control while 10 claimed to never use contraception. Only 1 teen reported a desire for pregnancy. When asked where they learned the most about birth control, 19 included a birth control clinic, 8 included a class or teachers in school and only 1 included doctors as important sources of information. When they last visited a physician or nurse, 14/35 remembered discussing pregnancy prevention.

In conclusion, children in the foster care system are at high risk for teen pregnancy. Preliminary results suggest that teens rely on educational programs in school and birth control clinics for information on pregnancy prevention. There are many missed opportunities to discuss this topic during health care visits. We should devote more time and resources to meeting their needs as most of them wish to avoid teenage pregnancy.

Emotional Adjustment in Adolescents Entering Foster Placement

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Placement in foster care and group homes is being used increasingly by public agencies for adolescents in need of substitute care. The circumstances that lead to children's placement in substitute care render them at risk for psychologic disorders. The purpose of this study was to evaluate the emotional state of adolescents entering foster placement.

Thirty-two adolescents entering foster placement completed the Children's Depression Inventory, the Nowicki-Strickland Locus of Control Scale for Children, the Piers-Harris Self Concept Scale, a brief structured interview and physical examination.

Children ranged in age from 14 to 17 years, 56% were male, 86% were African-American. Two-thirds of the children had experienced previous foster placements, with an average duration of placement of 15.3 months. Subjects had a more external locus of control as compared with instrument norms ($t=4.05$, $p=.0003$), suggesting a belief that outcomes are contingent on fate, chance, or powerful others, rather than on one's own actions. This finding was consistent when analyzed for females ($t=2.41$, $p=.032$), males ($t=3.50$, $p=.003$), and for different age groups. An association was found between increased duration of placement and external locus of control (Chi square $=27.28$, $p=.038$). Study children scored within normative limits on depression and self-concept scales.

External locus of control orientation may reflect loss of control felt by these children due to family instability or prior foster care experience. The lack of evidence for depression or diminished self-concept in this group may be related to compensatory mechanisms developed to cope with this loss of control. Further study will help to delineate his apparent discrepancy and to develop interventions more specific to the emotional needs of these children.

Parental Stress and Children With Hemangiomas

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Hemangiomas are the most common benign tumors of childhood. They present at birth or shortly thereafter with a raised, often colored lesion, and rapidly enlarge before involuting over a period of many years. Parents are often shocked by the unexpected appearance and rapid growth of the lesion. The medical community has paid scant attention to the psychosocial needs of these parents and their children as most hemangiomas are not immediately life-threatening. The purpose of this study was to address the psychosocial needs of this population within the context of a parental support group. Twelve parents of children with hemangiomas met with four faculty to discuss their concerns about their child's hemangioma. Measures obtained from each parent at the initial session included (1) the Mental Health Inventory (MHI) and (2) a specially-constructed questionnaire eliciting family demographics, medical history, and perceptions of the hemangioma and its effects. As a group, these parents scored significantly lower than the general population on the Psychological Well Being ($p=0.002$) and the global Mental Health Index ($p<0.05$) of the MHI. Larger hemangiomas were associated with parental perception of greater changes in their lifestyles. These parents believed they were more upset ($p=0.025$), had less time for recreation ($p<0.001$) and sustained greater work changes ($p=0.03$) than parents of children with smaller hemangiomas. Parents whose child's hemangioma caused visceral complications perceived themselves to be more upset than parents of children without visceral complications secondary to their lesions ($p=0.0074$) and were less likely to hope for complete regression of the lesion ($p=0.03$). This study suggests that these parents may be more stressed than previously thought and psychosocial intervention may be helpful to these families during the early childhood years.

Does Maltreatment Beget Maltreatment?

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It is widely believed that parents who were abused during childhood are more likely to abuse their own children compared to parents who were not abused. To assess the available scientific evidence, we reviewed studies published in English that provided information about physical maltreatment in two generations and included a comparison group. Of the 8 studies (4 cohort, 1 cross-sectional and 3 case-control), the relative risk of maltreatment of the children of parents who were abused during childhood was increased in 6 studies and not increased in 2 studies.

Salient methodological issues that could affect the generalizability or validity of these results were identified. There was marked variability in the definition of abuse (from being hospitalized for abuse to simply being spanked) both as the risk factor and as the outcome. There also was marked variability in the sources used to detect abuse (from self-report to court records). Problems of recall bias (7 studies) and detection bias (6 studies) were sometimes not addressed. Subjects included both parents in 5 studies, but only the mother in 3. There sometimes were differences in the index and comparison groups in important confounders such as SES (2 studies), and family structure (3 studies). Four studies failed to ensure that comparisons were not themselves maltreated. Only 4 studies clearly indicated whether the enrolled parent actually was responsible for the maltreatment. Only 1 study controlled for major interventions (e.g., foster care).

In summary, there are major methodological short-comings in all studies. We conclude that the current data are insufficient to support or to refute the belief that maltreatment begets maltreatment.

Psychosocial Characteristics of HIV-Infected Families

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Parental HIV infection has been extensively studied with regard to perinatal transmission, but few studies have examined the emotional impact of parental infection on noninfected children. We describe the psychosocial characteristics of a sample of USAF families in which one or both parents has early stage HIV-infection. 20 families with a total of 31 non-infected children completed standardized questionnaires designed to measure psychological profiles of parents and children, and to assess perceived stressors and sources of social support. Compared to questionnaire norms, parents in 35% of families had significantly (>1.5 SD) high scores for anger and/or depression on the Hopkins Symptom Checklist. Family Environmental Scale scores indicated a sig (>1.5 SD) lack of internal support and/or increased conflict in 45% of families. 30% of mothers with young children (5/15) reported dysfunctional relations with their children on the Parenting Stress Index. Although only 40% of families listed HIV as significant stressor, 45% reported inadequate social support. Despite family stress, only 15% ($N=27$) of children had abnormal scores on the Child Behavior Checklist. In summary, relatively healthy HIV-infected parents experience significant family dysfunction and stress, yet report few problems in their children. Comparison of this sample to families with parental malignancy, and to a matched, noninfected control group is in progress to help delineate HIV-specific effects.

Intussuception: A Spectrum of Presentations

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Intussusception is the most common cause of intestinal obstuction in the pediatric population ages 3 months to 3 years. The incidence ranges from 0.5 to 4 per 1000 live births. Classically, intussusception presents with vomiting and episodic cramping abdominal pain. These episodes are separated by intervals wherein the patient may be entirely comfortable. Although stools may be normal at first, bloody stools usually follow within the first twelve hours. If severe, the infant usually passes the characteristic "currant jelly" stool. Frequently however, the presentation of intussusception does not conform to this classic picture. We report our experience with six children between the ages of 3 1/2 months and 9 3/4 years presenting to the Children's Hospital Emergency Department in Seattle. This series of cases illustrates some of the varied presentations which may confuse and delay the diagnosis and treatment. One of the cases also emphasizes the grave complications that can be associated with this disorder.

Heparin Therapy May Limit Skin and Extremity Necrosis in Meningococcal Purpura Fulminans

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Meningococcal purpura fulminans (PF) is associated with necrosis of extremities and skin in those patients who survive. We hypothesized that heparin therapy may reduce the incidence of skin and limb necrosis due to its inhibition of the clotting cascade and its ability to prevent the Shwartzman reaction. To test this hypothesis, we reviewed the charts of 25 patients with PF associated with meningococcal disease. Our study population was comprised of 14 patients who survived at least 48 hours in whom we could evaluate extremity and skin necrosis. Clinical, demographic and outcome data were compared between patients who received therapeutic heparin therapy (50-100 u/kg bolus followed by a continuous infusion) in the initial 72 hours (3 patients) and those who did not (11 patients). Demographic and initial laboratory findings, including mean age (22 vs 38 mo.), male/female ratio, mean temperature (40.9 vs 39.7 C), mean systolic blood pressure (78 vs 80 mm Hg), mean arterial pH (7.41 vs 7.37), mean arterial pCO_2 (24 vs 23) were similar between groups ($P>0.05$). White blood cell count was lower (3.9 vs $7.8 \times 10^9/L$) and fibrinogen (265 vs 133 g/L) was higher in the group treated with heparin, but did not achieve statistical significance. In all three patients who received therapeutic heparin, and in 8 of 11 paients who did not, purpura were noted diffusely on the trunk, arms and legs on admission. When these patients were compared for dermatologic and orthopedic sequelae, the mean number of digits (6.3 vs 16.4; $P=0.03$) and extremities (1.7 vs 3.7; $P=0.03$) with necrosis was greater in those patients who received no heparin or subtherapeutic doses.

We conclude that heparin may limit skin and extremity necrosis when used early and in therapeutic doses in meningococcal purpura fulminans.

Adolescent Pregnancy: The Hidden Agenda

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117 adolescent females from an urban pediatric hospital with positive pregnancy test results over a five year period were retrospectively reviewed. The mean age was 15 years with 12 patients $\leqslant 13$. Presenting complaints varied greatly; 25% were totally unrelated to pregnancy. Fewer than 20% of patients requested a pregnancy test and only 30% of charts had documentation of sexual activity. 26% had physical exam findings consistent with pregnancy, only 37% had a pelvic examination. Of those with documented gestational ages, 28% were judged to be $\geqslant 13$ weeks and 17% were $\geqslant 18$ weeks. Patient age at presentation had no correlation with duration of pregnancy ($p=0.6$). Complications of pregnancy were rare and only 3% required hospital admission. 25% of patients diagnosed in the Emergency Department underwent procedures or received medications prior to diagnosis of pregnancy.

History, physical exam and presenting complaints are not helpful in diagnosing adolescent pregnancy placing the individual and fetus at risk for adverse effects of routine procedures and medical therapies. Health professionals should have a low threshold for pregnancy evaluation.

Back Pain in Children

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There is little data available about back pain in children, and many believe the symptom is rare. During a 12 month period, 232 children presenting to the ED with a complaint of back pain were evaluated prospectively using a questionnaire and lab tests as indicated. The median age was 12 years and 60% were female. Pain was most commonly located in the lumbosacral or thoracic area. Onset was acute ($\leqslant$one week) in 91%, and chronic($\geqslant$ 3 months) in only 4%. Pain awakened children from sleep in 39%, and caused 41% to miss school or work. The most common etiologies were direct trauma(25%), muscle strain(24%), sickle cell crises(13%), idiopathic (13%), and viral syndrome(6%). Spondylolysis was found in one patient, and pain was stress-related in 1%. Young children($\leqslant$ 12 years) were most likely to have direct trauma as the etiology, and older children($\geqslant$ 12 years) had pain most often due to muscle strain. Radiographs of the back were obtained in only 19% and were abnormal in 3%. Urinalysis were obtained in 47% and were abnormal in 11%. Of the 7% requiring hospital admission, almost 1/2 were attributed to sickle cell crises. Back pain is common in children; the cause of the pain is identified easily.

Referring Physician (RP) Utilization of Emergency Services: Enhancing Communication

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To determine their utilization needs, we surveyed RP who commonly refer patients to an urban pediatric emergency department (ED). Methods of communication with these RP were assessed. Of 227 RP surveyed, there were 140 responders (62%). Most (72%) utilized the ED for attending or subspecialty evaluation. Although 82% were satisfied or very satisfied with patient care, 50% were not satisfied with follow-up communication. The most common suggestion for improvement was that a return phone call be made to the RP (N=52, 37%). After the survey, RP were notified of a direct referral phone line. A permanent copy was kept of all referrals, and the ED attending physician made responsible for all follow up. A six month follow-up survey of the 140 RP and an additional 72 active RP was conducted. 108 of 127 respondents referred patients in the previous 6 months. 80% stated that follow up information in the past 6 months was either the same or improved. Awareness and utilization of the direct phone line improved twofold. We conclude that the ED provides a valuable service and that through simple measures, communications with RP can be improved.

A Prospective Evaluation of Esophageal Coin (EC) Management

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To study non-invasive initial management of EC in children, we prospectively evaluated children presenting consecutively to a pediatric ED after coin ingestion. All children received a physical and x-ray examination. Asymptomatic children over two years were (with informed consent) observed either at home or in the hospital while all others were hospitalized. Children not taken directly to the operating room had repeat x-rays within 24 hours of ingestion in order to detect coin movement. Impacted coins were then removed via endoscopy.

During 24 months, 130 patients were enrolled, of which 123 (94.6%) had x-ray evidence of a swallowed coin. 73 (56.2%) had EC: 34 (46.6%) at the thoracic inlet, 22 (30.1%) at the aortic arch, and 17 (23.3%) at the GE junction (GEJ). 45 of the 73 patients with EC were either observed at home or in the hospital. 23 (51.1%) of these coins passed beyond the esophagus within 24 hours of ingestion. GEJ coins passed more often than others (O.R. = 16, 95% CI 2.5-126). Our data suggest that in an asymptomatic child, observation reduces need for endoscopic removal of an EC.

Febrile Infants With Pleocytosis: Early Identification of Non-Bacterial Disease

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Many physicians advocate spinal fluid analysis as part of a routine sepsis work-up for febrile infants. Once an abnormal cerebral spinal fluid (CSF) profile is obtained, differentiation of bacterial from viral disease is often difficult. We analyzed several CSF and serum tests in 74 febrile 1-2 month old infants with CSF pleocytosis, attempting to identify a subgroup of children with non-bacterial meningitis who could be managed without antibiotics. All children had a CBC, serum glucose, and CSF glucose and protein measured as part of their sepsis work-up. Those with a CSF/serum glucose ratio > 0.4 and band/(band + neutrophil) ratio < 0.2 and CSF protein < 80 were considered to be test positive. Of the 74 children studied, 66 had aseptic meningitis, based upon negative CSF and blood cultures. 34 (52%) of the 66 were test positive. None of the eight patients with bacterial meningitis were test positive. We conclude that in infants with CSF pleocytosis, simple analysis of lab tests will identify a large proportion of those with aseptic disease.

Government Health Insurance in Two Societies

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Black West Philadelphians (BWPs) and Han Chiese Beijingers (HCBs) are 2 ethnically homogeneous groups with similar mortality characteristics both covered by government insured medical care. In order to compare knowledge of minor medical problems and utilization of the emergency department (ED) in these 2 populations, we surveyed patient families in the resident clinic at both CHOP (N = 49) and BCH (N = 39). Both groups found it relatively easy to access the ED, yet HCBs were less frequent visitors (56% to 69%, $p \leqslant .05$) for colds and fevers. Both groups were able to appropriately identify scenarios requiring ED services. In spite of the lack of telephones and regular pediatricians along with a similar understanding of mild medical problems, HCBs still utilized the ED less often than their BWP counterparts. Uniform, free government-sponsored health care need not translate into increased ED utilization, and sociocultural variables are likely at work to promote ED usage.

Ethanol Ingestion and Trauma in a Pediatric Emergency Department

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Ethanol is the psychoactive drug most commonly abused by children and adolescents. However, the majority of information associating ethanol ingestions with trauma in the emergency department setting is derived from the adult literature. In order to determine if ethanol ingestions are associated with a history of trauma in the pediatric emergency department setting, we reviewed the toxic screens of all patients presenting to the emergency department of a large, urban children's hospital over an 18 month period. Ethanol was identified in the blood and/or urine of 59 patients. Charts were available for review in 50 of these patients. Two children were younger than 12 years of age and were excluded from analysis. The mean age was 17.9 years (range 12.8-31.9). Forty-two percent of patients were female. The mean serum ethanol concentration was 324 mmol/L (1492 mg/L), with a range of 26-1092 mmol/L. A diagnosis of trauma was obtained in 48% of cases. However, there was no significant difference in the serum ETOH concentration between the trauma and non-trauma groups (student's t-test). Male patients were more likely to have a history of trauma than female patients as determined by chi square analysis ($P = .01$). 54% of patients were discharged from the emergency department, 28% were admitted to the general medical or surgical ward, and 18% were admitted to the intensive care unit. Two patients were hypoglycemic on presentation (serum glucose < 2.8 mmol/L). No patients required dialysis; there were no fatalities. This review suggests a higher than expected percentage of females with a positive blood ethanol level than in the adult emergency department population. However, the male predominance of those patients presenting with injury is similar to the adult emergency department experience. These data also suggest that ethanol may be a factor in more childhood and adolescent trauma than expected.

Cholesterol Reduction: A College Based Approach

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Since atherosclerosis begins in childhood and cholesterol levels track from adolescence to adulthood, early intervention may be important. We conducted an experimental trial to test the effectiveness of a health education intervention aimed at reducing the serum cholesterol levels of college students. Thirty-nine subjects with serum cholesterol confirmed by a research lab to be $\geq$ 75th percentile were randomized to two study groups: Group 1 ($n = 16$) received only a lecture on cholesterol and nutrition. Group 2 ($n = 18$) participated in seven weekly sessions on nutrition and behavior modification. All completed pre- and post tests assessing knowledge and attitudes. At study completion, all had two lipid profiles analyzed. The groups did not differ at baseline on any measure. However at post-test, Group 2's knowledge ($p = .02$) and attitudes ($p = .08$) had improved more. One-third ($n = 6$) of students in Group 2, but only 6% ($n = 1$) student in Group 1 had follow-up cholesterol levels $\leq$ 75th percentile ($p = .06$). Group 2 students made more behavioral changes as a result of our intervention which, if sustained, may reduce their risk of future coronary artery disease.

School Level Interventions and Correlates of Child Bicycle Helmet Use

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To test the utility of school level interventions for child bicycle safety and to identify social and behavioral factors associated with child bicycle helmet use, we conducted a two level intervention in two suburban elementary schools. Children ($N = 209$) and parents ($N = 125$) in school 1 and in school 2 (child $N = 470$, parent $N = 364$) were surveyed regarding bicycle injuries and helmet use. Children and parents in 1 and 2 received bicycle safety literature and discount coupons for helmet purchase. School 1 was then the target of an intensive safety campaign, including meetings with the school safety committee and the PTA and a classroom presentation to children emphasizing helmet use. Ten months later the same survey was again administered. Children in 1 were more likely at post-test to believe that helmets were protective ($p = 0.003$) but did not differ on other variables. Using logistic regression, sibling helmet ownership, parental helmet use, and lower parental perceived social barriers to helmet use were independently associated with children's reported helmet use and with parental intent for the child to use a helmet at post-test.

Value of Urinary White Blood Cells in Identifying Adolescents With Chlamydia Trachomatis Urethritis and Cervicitis

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Many clinicians use urinary leukocyte esterase and microscope urinalysis for white blood cells as screening tests for sexually transmitted disease. We assessed the value of microscopic urinalysis for white blood cells in identifying C. trachomatis infections in a high-risk sample of adolescents.

41 subjects with high-risk sexual histories (16 girls and 25 boys; age of 17.7 ± 1.5 years) were recruited for entry into an antibiotic efficacy study. 23 subjects had had positive C. trachomatis cultures within the last five days, 12 subjects had positive rapid tests for Chlamydia, 4 subjects were contacts of persons with Chlamydia infections, and 2 subjects had clinical signs of sexually transmitted disease. 32 (78%) of the subjects were asymptomatic. Subjects were cultured or recultured for C. trachomatis and urine specimens were obtained for microscopic urinalysis. Any urine value greater than 1 white blood cell per high powered field was considered positive.

26 of the 41 subjects (63%) had positive cultures; of these only 12 (46%) were positive for urine white blood cells. Sensitivity of the microscopic urine for the white blood cells was 46%, specificity was 73%, positive predictive value was 75%, and negative predictive value was 44%. If microscopic urinalysis had been the only screening parameter, 14 (54%) of the 26 positive cases would have been missed. All of the female subjects had positive cultures. 8 of these positive cases would have been missed by microscopic urinalysis alone. Of the 26 male subjects, 10 (40%) had positive cultures. 6 of the 10 positive cases would have been missed by microscopic urinalysis alone.

In populations at high risk, microscopic urinalysis for white blood cells is a poor single screening test for C. trachomatis infection.

The Impact of Anti-Drug Advertising on Youth Substance Abuse

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Anti-drug advertising aimed at youth receives over $1 million of support daily, yet its effectiveness in deterring substance abuse is uncertain. To assess the perceived impact of these ads on drug use knowledge, beliefs, attitudes, and behavior, we administered an anonymous questionnaire to 849 public school students aged 11-19 years (50% male; 47% white; 51% suburban). Lifetime prevalence rates for use of alcohol and use of other drugs (marijuana, cocaine, or inhalants) were 59% and 21%, respectively.

Overall, 81% recalled exposure to the ads. Among the exposed subjects, 93% gained knowledge about drugs, 58% developed stronger beliefs about drugs' dangers, and 51% became less willing to be friends with users. Of those who have not tried alcohol or other drugs ("nonusers"), 86% were convinced never to start; of those who have used alcohol alone, 73% were convinced never to try other drugs. In addition, 50% of the subjects who have used other drugs reported that ads caused them to decrease or stop use.

We conclude that anti-drug ads were perceived to have the desired deterrent effect by most "nonusers" and users of alcohol alone, as well as by many users of other drugs.

How Do Caregivers Define Potty Training?

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Potty training, an important milestone for children, is also a common precipitator of child abuse. In order for pediatricians to best communicate with families regarding this often emotionally laden topic, we must understand what parents mean by "potty trained."

A cross-sectional survey study was conducted at the OSU Pediatric Practice. One hundred and seven (107) care givers accompanying young children were surveyed regarding issues of parental expectations, physician's role in educating parents, accidents, child's independence in toileting, and demographic variables.

Our results demonstrated that the term "potty training" has a wide range of definitions. Children requiring assistance in going to the toilet and having accidents were often considered to be potty trained. Caregivers more likely to want a physician's advice had completed more than 12 years of education and were caucasian.

In conclusion, the term "potty trained" has different meanings for different caregivers and is associated with a variety of expectations.

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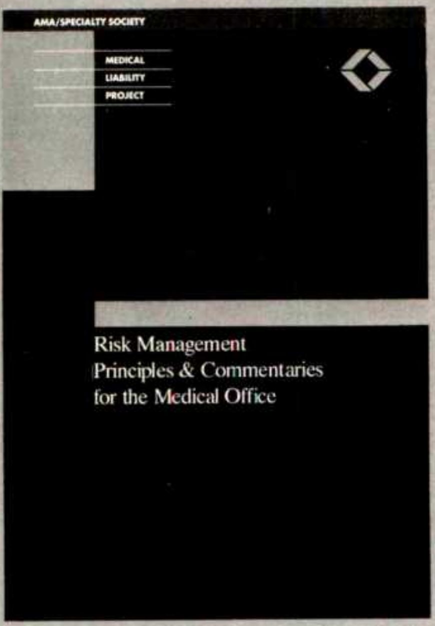

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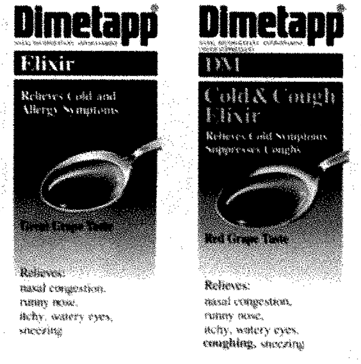

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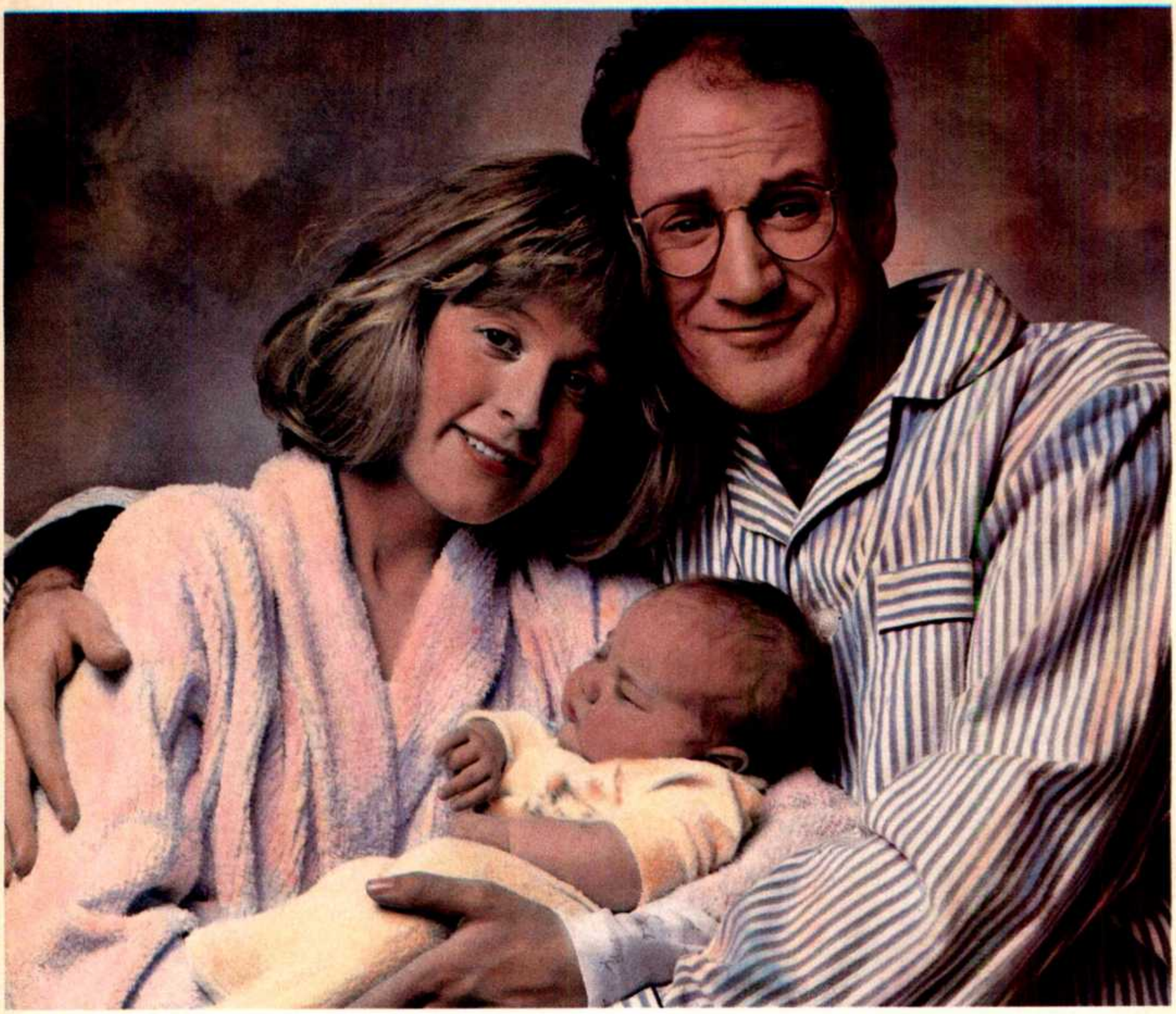

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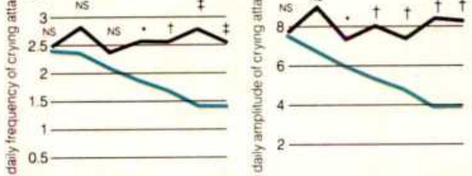

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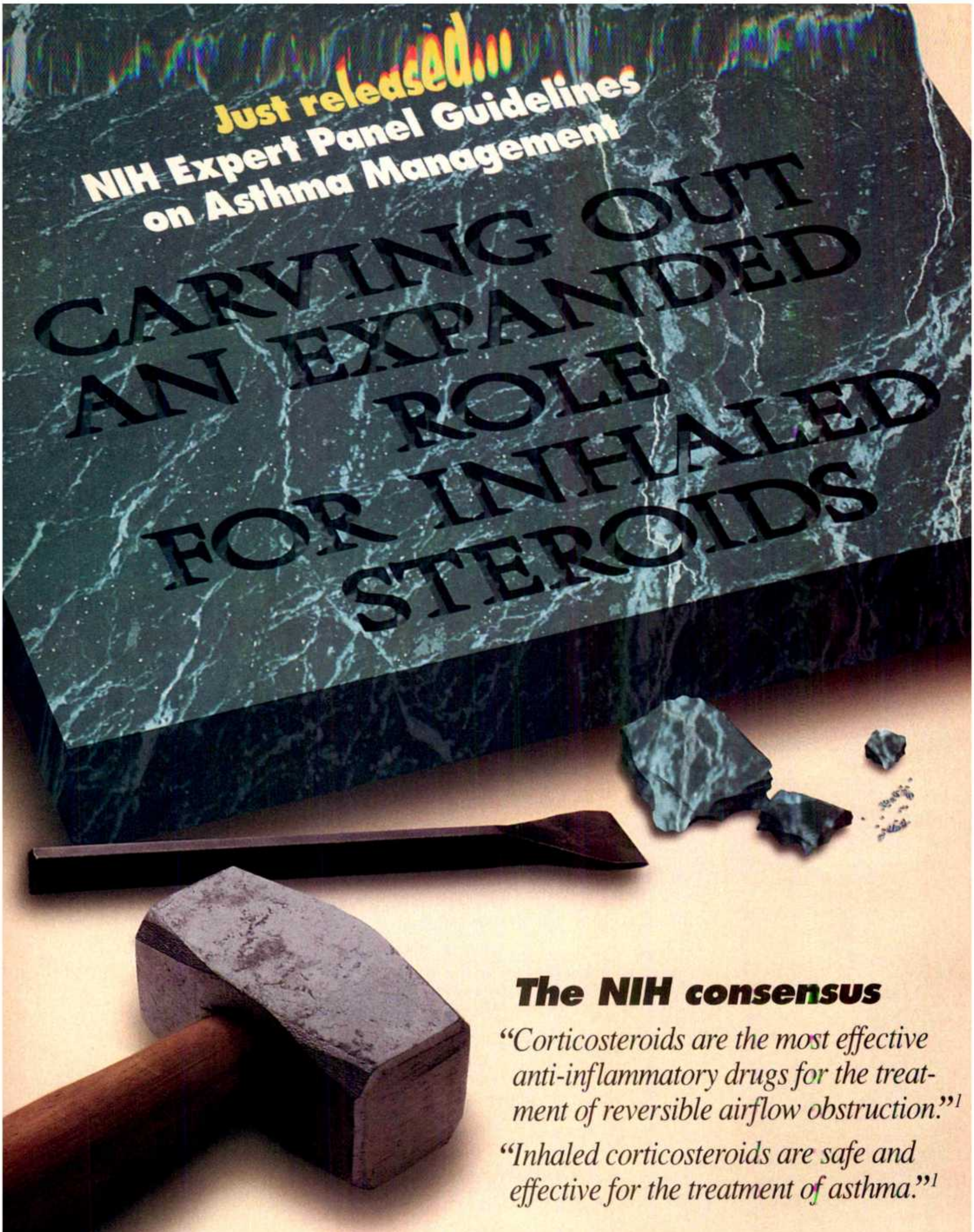

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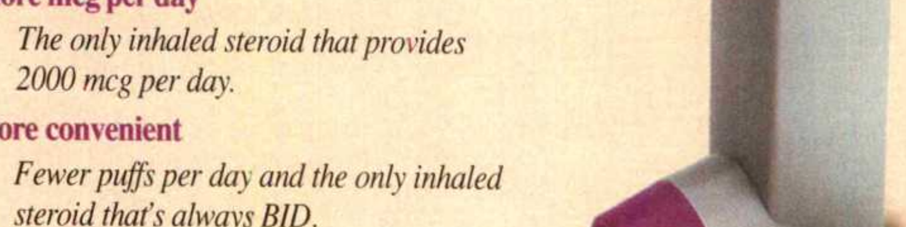

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Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with Candida albicans or Aspergillus niger have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral Candida may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler.

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function.

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice. An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors.

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General:* flu (10%); *Mouth and Throat:* sore throat (20%); *Nervous System:* headache (25%); *Respiratory:* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); *Special Senses:* unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations; *Gastrointestinal:* abdominal pain, heartburn; *General:* chest pain, decreased appetite, edema, fever; *Mouth and Throat:* Candida infection; *Nervous System:* dizziness, irritability, nervousness, shakiness; *Reproductive:* menstrual disturbances; *Respiratory:* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*; *Skin:* eczema, itching (pruritus), rash; *Special Senses:* ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; *Cardiovascular:* hypertension, tachycardia; *Gastrointestinal:* constipation, dyspepsia, gas; *Hemic/Lymph:* capillary fragility, enlarged lymph nodes; *Mouth and Throat:* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; *Nervous System:* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo; *Respiratory:* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort; *Skin:* acne, hives, or urticaria; *Special Senses:* blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath.

---

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

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1. *National Heart, Lung, and Blood Institute National Asthma Education Program Expert Panel Report—Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md: US Dept of Health and Human Services; 1991.
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While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

In Memoriam—Ray Eugene Helfer, MD

October 19, 1929, to January 27, 1992

Pediatrics and *AJDC* have lost, prematurely, a colleague and friend, Ray E. Helfer, MD. Ray's life was one of caring—for his family, his friends, his colleagues, his students, his patients, and the thousands of children, whom he never saw, but who benefited from his professional efforts in the area of child abuse and neglect.

Ray was associate editor of *AJDC* during the early years of my editorship, when he left us to become chief editor of the *International Journal of Child Abuse and Neglect*. However, he continued to review manuscripts and write several articles and commentaries for us,[1,2] the latest of which is published in this issue.[3] This article was accepted before his illness and was revised in part by him and in part posthumously by William Weil, MD.

The Helfers and the Fulginitis have been close friends for more than 34 years. Ray and I were residents together and at one time were on the faculty at the University of Colorado School of Medicine, Denver. Our wives, Shirley Fulginiti and Mary Edna Helfer, were nursing students together at Philadelphia (Pa) General Hospital. Our families retained close ties over the years. We all remember Ray's fine qualities and treasure his fine sense of humor, which kept us all in balance.

See also p 545.

Ray suffered a cerebral hemorrhage in Spain during a visit to his son, David. After an 8-week illness, including medical transport back to the United States, he died in East Lansing, Mich, on January 27, 1992. Ray is survived by his wife, Mary Edna, and his children, Sharon Lynn, Ray Jr (married to Sally, with three grandchildren, Daniel, Matthew, and Michael), Christopher, Jeffrey, Jennifer, and David.

Ray was an internationally respected clinician, teacher, and scholar. His contributions included innovations in medical education and advances in our understanding of the pathogenesis, diagnosis, and management of child abuse and neglect. Some of his most cogent observations were published in *AJDC*.[1-6] The development of simulated mothers to assist in medical student and resident education and evaluation was conducted in conjunction with his research assistant, Mary Black, and his wife, Mary Edna.[6] In the late 1970s, Ray and Mary Edna were invited to present the results of their research before the Department of Pediatrics, University of Arizona, Tucson, of which I then was chairperson. They taught their method to Paula Stillman, MD, who remains active in further development of the concepts initiated by them. His other outstanding contributions included innovative objective methods for evaluation of medical students and residents; development of statewide trust funds to support efforts in prevention of child abuse and neglect, which are now in effect throughout the country; and the comparison of infant-rearing in nonhuman primates to mother-infant interaction in humans, his latest endeavor.

Ray received his undergraduate education at Oberlin (Ohio) College and his medical degree from Upstate University of New York at Syracuse. He completed his internship at Philadelphia (Pa) General Hospital, and his residency at Temple University's Department of Pediatrics, at St Christopher's Hospital for Children in Philadelphia, Pa. He also earned master's degrees in pediatrics (Temple University, 1961) and education (University of Illinois, Chicago, 1968). Ray was a faculty member of Temple University, the University of Colorado, Denver, and Michigan State University's College of Human Medicine, East Lansing. At the University of Colorado, he was a colleague and collaborator of C. Henry Kempe, MD, a pioneer in the field of child abuse and neglect, and he worked with Ruth Kempe, MD, Brandt Steele, MD, Richard Krugman, MD, and others.[7] He was a faculty member at Michigan State University for 20 years, reaching full professorship; served for one term as acting chairman of the department of human development; and was associate dean for pre-clinical curriculum and student programs for 5 years.

Ray Eugene Helfer, MD

Ray was a sought-after consultant, lecturer, and mentor. He was a member of many prestigious national professional organizations and helped found the Ambulatory Pediatric Association, serving as president of the organization in 1972. He received many awards and accolades including the Genesis Award from the National Committee for the Prevention of Child Abuse, the American Medical Association Merit Award, the Brandt Steele Award from the C. Henry Kempe National Center for Child Abuse and Neglect, and the Distinguished Faculty Award from the College of Human Medicine, Michigan State University, East Lansing.

We will miss Ray Helfer. He has left a rich legacy of humanism and caring. His family has established a memorial fund, the Ray E. Helfer Childrens' Fund, which can be contacted at PO Box 1781, East Lansing, MI 48826. The purpose of the fund is to improve the health and well-being of children through pediatric education, services to children and families, and establishment of a children's medical center in the community.

VINCENT A. FULGINITI, MD
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CORRECTION

Erroneous Values in Table 2

In the article titled "Surfactant Replacement Therapy in Respiratory Distress Syndrome" published in the January 1991 *AJDC* (145:102-104), the authors have corrected the miscalculated values in four major subheadings in Table 2 on page 103. The numbers that are boxed in the reprinted table were incorrect in the original table.

Table 2.—Effect of Surfactant Replacement on the Outcome in the Selected Trials*

	Mortality, %			PDA, %			Pneumothorax, %			IVH, %			BPD, %		
Study	**S**	**C**	**RD, %**	**S**	**C**	**RD, %**	**S**	**C**	**RD, %**	**S**	**C**	**RD, %**	**S**	**C**	**RD, %**
Enhorning et al[8]	3	18	–15†	46	58	–12	15	33	–18	28	61	–33†	56	67	–11
Kwong et al[10]	7	15	–8	50	31	19	43	54	–11	36	31	5	43	69	–26
Gitlin et al[12]	17	26	–9	61	65	–4	17	57	–40†	89	74	15	22	30	–8
Raju et al[13]	18	46	–28	71	23	48†	12	46	–34†	47	62	–15	24	92	–68†
Kendig et al[15]	29	29	0	26	16	10	6	23	–17	24	16	8	35	35	–0
European[16]	31	51	–20†	60	46	14	18	35	–17†	47	55	–8	16	26	–10
Horbar et al[17]	17	17	0	1	48	–7	10	30	–20†	24	25	–1	45	44	1

*RD indicates rate difference; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; S, surfactant group; C, controls; and BPD, bronchopulmonary dysplasia.

†Indicates that the results were statistically significant (*P*<.05).

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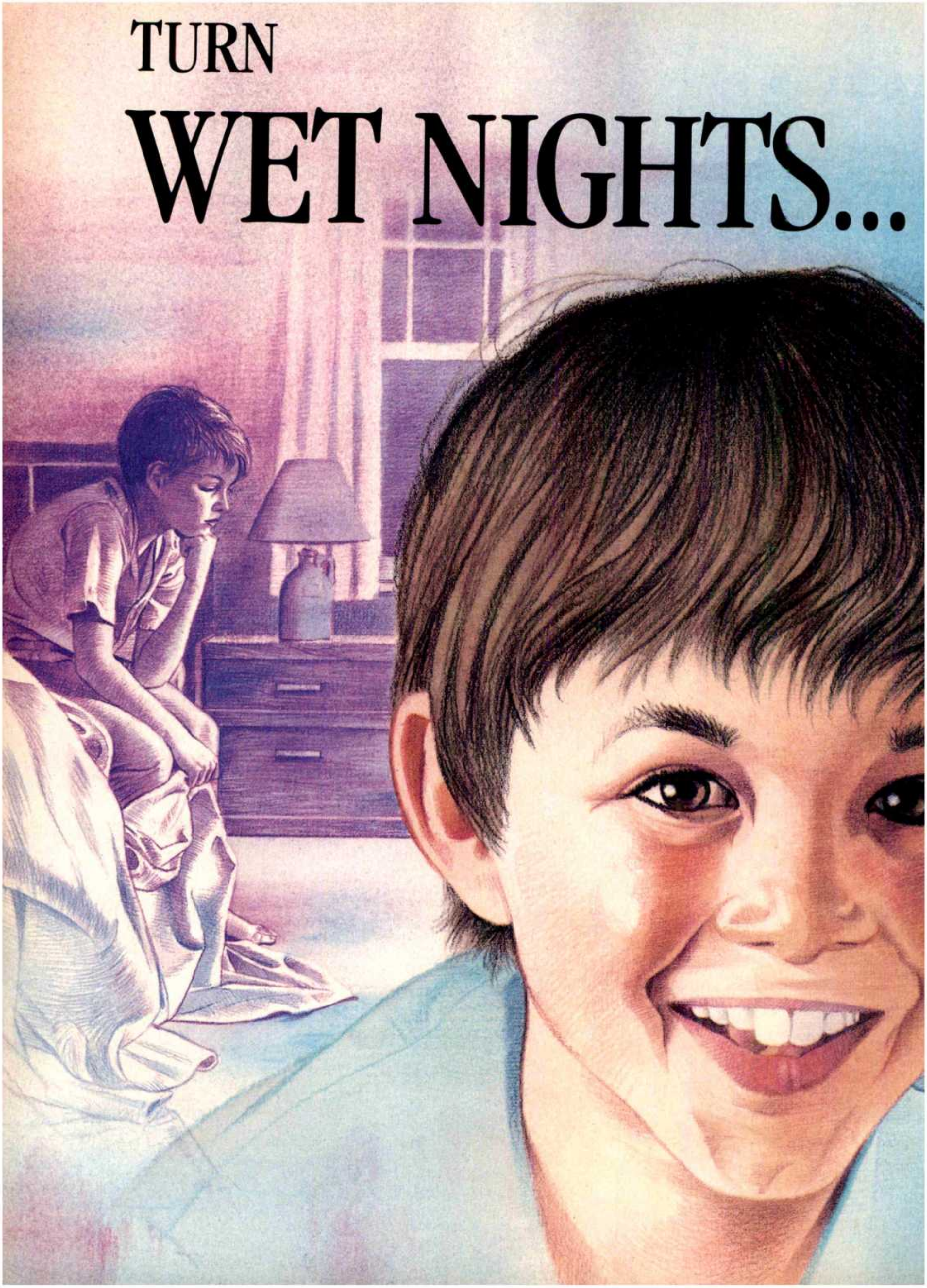
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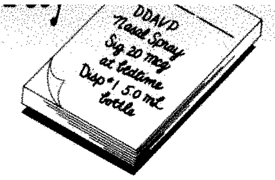

Brief Summary
CONTRAINDICATION: Known hypersensitivity to DDAVP Nasal Spray.
WARNINGS:
1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality and resulting seizures.
PRECAUTIONS:
General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.
DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.
Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used. For such situations, DDAVP injection should be considered.
Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP Nasal Spray should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.
Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.
Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities. No further information is available.
Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg.
Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.
Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.
Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nose-bleed, sore throat, cough and upper respiratory infections have also been reported.
The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

	PLACEBO (N=59)	DDAVP 20 mcg (N=60)	DDAVP 40 mcg (N=61)
ADVERSE REACTION	%	%	%
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.
HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see full prescribing information in product circular.

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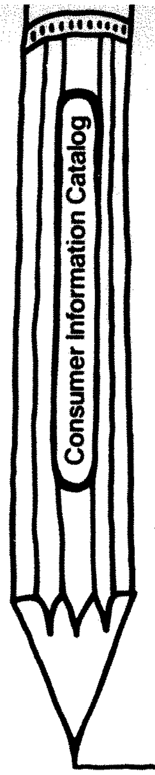

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The following letter, which appeared in the February 1992 issue of AJDC, *was mistakenly published without the table. It appears in its entirety below.*—ED

Intravenous Immune Globulin and Aseptic Meningitis

Sir.—We report the case of a patient with aseptic meningitis that was probably caused by the administration of intravenous immune globulin (IVIG).

Patient Report.—A 9-year-old boy was admitted to the hospital 1 day after the development of epistaxis and hematemesis. Results of physical examination were unremarkable except for petechiae on the palate. A complete blood cell count revealed a hemoglobin level of 99 g/L and a white blood cell count of 7.2×10^9/L, with 0.24 segmented neutrophils, 0.68 lymphocytes, 0.05 monocytes, and 0.03 eosinophils. His platelet count was 16×10^9/L, and a peripheral blood smear showed a decreased number of platelets and giant platelets. A clinical diagnosis of immune thrombocytopenic purpura was made. Intravenous immune globulin (400 mg/kg of body weight; Sandoglobulin IV, Sandoz Pharmaceuticals, East Hanover, NJ) was infused over 4 hours daily for 2 days. His platelet count increased to 69×10^9/L within 48 hours of starting infusion. Approximately 12 hours after completion of the second dose of IVIG, the patient complained of headache. He also developed fever and vomited once. Results of neurologic examination revealed the patient to be lethargic, with normal fundi but a stiff neck. A computed tomogram of the head was normal. Lumbar puncture revealed cloudy cerebrospinal fluid. Analysis of the cerebrospinal fluid revealed the following values: white blood cell count, 2.5×10^9/L (0.98 segmented neutrophils and 0.02 lymphocytes); protein, 0.60 g/L; and glucose, 4.1 mmol/L. A gram stain of the sediment was negative for bacteria, and viral (enteroviruses and herpes simplex) and bacterial cultures of cerebrospinal fluid were negative. Results of tests of renal and hepatic function were normal. Results of tests to detect antinuclear antibodies and anti-DNA were negative, and his C3 serum complement was normal. Administration of IVIG was discontinued after the second dose, and the patient began a short course of prednisone therapy (3 mg/kg of body weight per day for 4 days).

The patient became completely asymptomatic within 24 to 48 hours of the onset of neurologic symptoms. His platelet count was normal 4 days after hospitalization, and he was well at this writing.

Comment.—The clinical presentation and course of aseptic meningitis in this patient are similar to those in previously described patients.[1-3] Six episodes of aseptic meningitis, two in each of three patients, have been reported (Table). In four of these episodes, including that of our patient, headache, fever, and neck stiffness developed within 48 hours of administration of IVIG. In one patient, both episodes occurred 7 days after IVIG therapy, despite using a different IVIG preparation the second time. The white blood cell count in cerebrospinal fluid ranged from 0.18×10^9/L to 2.45×10^9/L, with greater than 0.90 neutrophils, an unusual finding in aseptic meningitis. All patients had rapid and complete recoveries.

The development of aseptic meningitis after IVIG administration in several patients with similar clinical courses adds supportive evidence to a causal relationship between the two; the mechanism of such a relationship is unknown. While headache, fever, and vomiting are reported to be frequent side effects of therapy with IVIG, what

Episodes of Aseptic Meningitis After IVIG Administration*

Source, y	Age of Patient, y	Diagnosis	IVIG Dose	Time Between Administration of IVIG and Symptoms of Meningitis	White Blood Cell Count, $\times 10^9$/L (Proportion of Segmented Neutrophils)†	Protein, g/L†	Comment
Jayabose et al,[1] 1990	6	Acute ITP	1 gm/kg	10 h after a single dose	0.35 (.94)	0.20	None
			1 gm/kg (two doses)	Within 24 h of second dose	0.18 (.85)	0.27	3-wk interval between the two episodes
Kats et al,[3] 1988	7	Chronic ITP	400 mg/kg (two doses)	36 h after first dose	2.45 (.88)	0.45	Similar episode 15 mo earlier‡
Casteels-Van Daele et al,[3] 1990	2	Acute ITP	400 mg/kg per day (five doses)	7 d after first dose	0.45 (.90)	0.15	None
			400 mg/kg	7 d	0.31 (.90)	0.21	3-wk interval between the two episodes
Present study	9	Acute ITP	400 mg/kg (two doses)	36 h after the first dose	2.50 (.98)	0.60	None

*IVIG indicates intravenous immune globulin; ITP, immune thrombocytopenic purpura. Viral and bacterial cultures were negative in all studies.

†In cerebrospinal fluid.

‡Patient's white blood cell count in cerebrospinal fluid was 1.55×10^9/L during the first episode of meningitis.

proportion of patients have laboratory evidence of aseptic meningitis is unknown. It is also of interest that all reported cases of aseptic meningitis occurred in patients with immune thrombocytopenic purpura and after improvement in platelet count.

Physicians should be aware that this clinical syndrome exists, that results of analysis of cerebrospinal fluid may be significantly abnormal in these patients, and that the outcomes reported to date have, to our knowledge, been uniformly good.

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A Second Look at Breast-feeding and Full-time Maternal Employment

Sir.—I used to be a full-time pediatrician; now I am a full-time mother and a part-time pediatrician. As a member of the "mommy club" (viz, the "old boys' network"), I chuckle at (and am embarrassed by) the advice I used to offer. For example, I used to believe that breast-feeding is, or should be, compatible with full-time maternal employment. Why not, you ask? Everyone does it. Articles and books are filled with advice on pumping and freezing milk, on avoiding "role overload," on the joys of "having it all" and of "quality time," and on the nutritional and immunologic benefits of breast milk. Success is measured by "duration of nursing." What could be missing?

Discussion of the infant's point of view and of the emotional side of the nursing relationship is usually missing. In fact, the entire mother-child relationship is usually tactfully ignored or relegated to a final paragraph that mentions the wonder of the occasional "real" nursing. Any consideration of the infant's feelings and needs is generally absent. Recall that full-time infant day care is a necessary corollary of full-time maternal employment. Surely *who* cares for the infant and how are as significant and worthy of discussion as what is placed in the bottle. One might also wonder if breast milk in a bottle from a mother substitute has significance for the infant as it does for the mother. Does this pattern of feeding permit and help the infant to know and make a relationship with his or her mother?

When an infant is nursed, his or her hunger and mother's let-down become synchronized (after about 6 to 8 weeks), forming the physical basis for the closeness and gratification of the nursing relationship. It is confusing and mistaken to use the word *breast-feeding* for both nursing and for the pairing of lactation (the maintenance of a milk supply) with breast-milk-in-a-bottle feeding by substitute care-givers. Most published work on combining breast-feeding and employment unfortunately neither entertains these issues nor steps beyond the confines of the technical aspects of the enterprise.

I fear my views are so unpopular and are rejected so vehemently because they provoke guilt. Finances and careers are usually more flexible and negotiable than we care to admit. What if all this mother-infant separation and substitute care (the "hidden" side of "breast-feeding" and working full-time) are neither necessary nor best for the infant? We often hear about the busy professional who "has to work." But pumping or no pumping, saying, "oh, it must be nice to be at home" to an at-home mother implies a self-sacrifice that simply is not there. In fact, staying home full-time is difficult, does not earn money or build self-esteem like work does, and can regularly make one feel isolated and "stir crazy," longing for the adult world of work where time flies. The gratifications of being at home are primarily long-term. One hopes that the dependable, consistent, and nurturing relationship one provides, though imperfect, is the best building block an infant can use to become a solid, mature person.

The end of nursing, too, is a time when it is difficult not to "need to be back at work." Weaning is a special and challenging period for mother and infant. It marks the end of a special closeness and the emergence of the infant as a person. Permitting the infant to reject the breast and supporting his or her growing away are extraordinarily difficult for most mothers. Pumping milk until one is either tired of it or until the infant is a certain age both sadly bypass an entire developmental step for both partners.

Unfortunately, breast milk cannot substitute for parenting (I can hear the cries of indignation already) and our current enthusiasm for combining lactation and separation may serve to divert attention from more substantive issues. For example, how can we as professionals and as individuals better support mothering, parenting, and the mother-child relationship? What economic incentives, from paid maternity leaves to child allowances to flexible hours with job security, would be most workable? What program of emotional supports (for mothers of all socioeconomic groups) from home visiting to parenting centers, would be best, and how could it be funded? I am certainly a strong advocate of nursing, but until our discussions move beyond breast milk to the mother-child relationship, I fear we are missing the forest for the trees.

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Fluid Management and Arginine Vasopressin in Bacterial Meningitis

Sir.—Padilla and colleagues[1] recently reported that urine vasopressin concentrations fell during the first 3 days of treatment of bacterial meningitis when patients received maintenance fluid requirements containing a mean of 5.6 mEq/kg per day of ionized sodium. In a similar series of patients,[2] plasma arginine vasopressin normalized within 24 hours when maintenance plus replacement fluids (the mean volume of fluid administered in a 24-hour period was 1.5 × maintenance and contained 7.8 mEq/kg per day of ionized sodium) were given, but remained elevated when fluids were restricted (the mean volume of fluid administered in a 24-hour period was

0.63 × maintenance and contained 2.2 mEq/kg per day of ionized sodium). The data presented by Padilla et al[1] appear to corroborate the earlier study,[2] but their article does not address the *temporal* relationship between changes in plasma arginine vasopressin concentration and changes in urine vasopressin concentrations.

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1. Padilla G, Ervin G, Ross MG, Leake RD. Vasopressin levels in infants during the course of aseptic and bacterial meningitis. *AJDC.* 1991;145:991-993.
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In Reply.—We cannot correlate changes in plasma and urinary vasopressin levels since we did not measure the former. However, urinary vasopressin levels reflect an integrated value for vasopressin changes in plasma. Urine vasopressin would be expected to have a close, temporal relationship with plasma arginine vasopressin levels during the interval since the last voiding.

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Working Hours for Pediatric Residents

Sir.—Now that the regulatory change in New York State restricting the number of hours worked by resident physicians has been in existence for more than 2 years, the article by Cheng[1] is timely and interesting. But "what the residents want" may not be "what the residents get or should get."

Continuity of care remains the most important characteristic of high-quality patient care[2,3]; it is the best and only way the physician can remain familiar with pertinent data concerning a patient's illness. This is particularly true when unexpected problems arise. A very dangerous situation exists when a patient develops an unexpected complication at night or on a weekend when the physician in charge is off duty. This lack of continuity of care consequent to the regulatory change in New York State not only poses a hazard to the patient but also proves detrimental to the education of the house staff. One learns only by following the day-to-day progress of a patient when his or her condition changes for better or worse, whether at night or on a weekend.

Regarding the issue of "moonlighting," the argument seems to me to be a paradox. If house staff members are so "overworked," how could they find time and energy to moonlight? So it is beyond my comprehension to fathom the rationale of restricting moonlighting if working hours are also limited.

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1. Cheng TL. House staff work hours and moonlighting: what do residents want?: a survey of pediatric residents in California. *AJDC.* 1991;145:1104-1108.
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In Reply.—I agree with Dr Cheng's comment that "what the residents want" may not be "what the residents get or should get." However, house staff views on the stresses they face are crucial to the discussion of work hours and to the formulation of strategies to reduce stress, promote education, and provide quality patient care.[1]

The need for "continuity of care" for optimal patient care and resident education has often been raised as an argument against work hours regulation. Discontinuity is inherent in our system, however; physicians cannot remain in the hospital indefinitely. The tradition of 36-hour (or longer) shifts is not grounded in science. Discussion of continuity inevitably involves discussion of hours.

The question is clear: what is the optimal number of work hours to maintain continuity, and how is this number decided? In the survey, respondents often commented that the current level of continuity and the current number of hours worked were not optimal, but were often *detrimental,* to both patient care and medical education. While the optimal number of work hours will vary from person to person, the survey demonstrated that most respondents strongly favor hours limits. The need for house staff input in the search for effective policy on continuity and hours should be clear.

Continuity of care is not an end in itself, but a means to the ends of high-quality patient care and medical education. Evidence that our current notions of continuity have not kept pace with changes in the medical profession, thus possibly compromising those goals, must be taken seriously.

Though it may seem a paradox that house staff want both limits on hours and moonlighting freedom, it is important to understand who moonlights and why. Dr Cheng asks how residents can moonlight when they are supposedly overworked. One study[2] has found that, while many residents moonlight, most residents work relatively few hours and concentrate those hours during less demanding rotations. It is important to look at *how* residents fit moonlighting activities into their work schedules.

Like most other employees, many respondents desired the freedom to spend their off-hours as they please. Most jobs, however, require many fewer hours worked. That residents desire both unrestricted free time and reasonable hours is understandable.

Recognizing that it may be necessary to choose between the freedom to moonlight and limits on hours, the survey asked "Which would you rather see: house staff work hours limited inclusive of moonlighting hours or no restriction on house staff working hours?" By a ratio of more than 2:1, respondents were willing to restrict moonlighting if resident working hours were limited. This underscores residents' desire for restrictions on hours, even at the expense of moonlighting.

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1. Cheng TL. House staff work hours and moonlighting: what do residents want?: a survey of pediatric residents in California. *AJDC.* 1991;145:1104-1108.
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Please see following page for brief summary of prescribing information.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risks of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDS even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension. Ibuprofen can inhibit platelet aggregation and prolong bleeding time.

CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions. Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: *Coumarin-type Anticoagulants:* Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H_2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 6 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS). Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain,* fullness of the GI tract (bloating and flatulence); heartburn,* indigestion, nausea,* nausea and vomiting; dizziness,* headache, nervousness; pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis; alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis, fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coomb's positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (eg., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness; renal papillary necrosis.

* Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children), 400 mg every 4-6 hours (adults).
Mild to moderate pain in adults: 400 mg every 4 to 6 hours.
Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses.
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References:
1. Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989; 46: 9-17.
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The Role of General Pediatrics in an Academic Department

Ray E. Helfer, MD†

In 1961, on completion of a chief residency in pediatrics, becoming the assistant director of the Outpatient Department at St Christopher's Hospital, Temple University, Philadelphia, Pa, was *not* considered by most to be a prestigious academic position. "A true academician would become a neurologist, cardiologist, or some other legitimate subspecialist," was a frequent reminder. Despite these jibes, one's commitment, and even devotion, to Dr Waldo Nelson made the decision to assume this faculty position, under the mentorship of Dr Richard Olmsted, very easy to accept. Even the salary of $11 000 per year seemed excessive after the lean residency years.

Primary care or even *ambulatory care* were not common jargon in those years and we "OPD [outpatient department] pediatricians" found ourselves apologizing and defending our positions.[1] The first meeting of the Ambulatory Pediatric Association (APA) in 1963 was held in Atlantic City, NJ, in conjunction with the American Pediatric Society and Society for Pediatric Research. The 50 pediatricians who attended the APA meeting had to wear name tags of a different color than the rest of the participants, lest we be confused with the "real" academicians. This policy continued until the early 1980s.

See also p 533.

By 1973, APA membership had grown to more than 500. I served as APA president that year, and the goals were to run "the best research-oriented meeting possible," and foster ongoing discussions with our colleagues in the Society for Pediatric Research and the American Pediatric Society. Working for the acceptance of general pediatrics/ambulatory care as a legitimate academic discipline was a constant activity of many academicians. The succeeding APA presidents have been successful in this endeavor. At the 1991 academic meeting, 30 years after Dr Nelson's offer to me to join his faculty, some 4000 academic pediatricians were in attendance, about one third of whom were associated with the APA. All were wearing the same color name tags.

Clearly, what those 30 years have taught us is that the general pediatrician in academia has a significantly different role than does the general pediatrician in clinical practice. While our background, basic residency, and clinical abilities are very similar, the roles differ as a result of the varying expectations of the university. The latter often requires fellowship training in research and teaching, responsibilities that go beyond those of a pediatrician in clinical practice.

This postresidency training, followed by many years of experience in a university setting, often results in opportunities to assume a variety of administrative positions in a medical school. The broad experiences and comprehensive nature of one's background make the academic generalist particularly suited for these positions.

Complete acceptance into the academic arena has not been, and is not, universal for the "academic generalist." Some still think of that phrase as an oxymoron and of the academic generalist as a second-rate faculty member, at best. Haggerty,[2] a true advocate, reviews the return of this endangered species in a recent review.

The debate continues. Since this article was first drafted, Taussig and Ey[3] penned commentary on Haggerty's article, in which seven questions were raised. These were answered with results of a survey, conducted by Haggerty, of the six participating sites of the "General Pediatrics Academic Development Program."[4]

This summary of the role of general pediatrics in an academic department was first written for our department and college faculty who, over time, had begun to equate "primary care" with "general pediatrics."

THE SEVEN FUNCTIONS OF A GENERAL PEDIATRICS UNIT WITHIN AN ACADEMIC DEPARTMENT

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General pediatricians are expected to teach at every level within the academic environment. At the preclinical level, they teach classes and seminars on growth and development, behavioral and developmental deviations from normalcy, clinical skills, interviewing, and clinical problem solving. At the clinical level they teach elective courses and have a teaching function in clerkships. General pediatricians also teach postgraduate level-1, level-2, and level-3 residents ambulatory care, newborn medi-

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†Dr Helfer died on January 27, 1992.

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Purpose of Primary and Secondary Care in an Academic Department

What Primary and Secondary Care Are	What Primary and Secondary Care Are Not
Resources for modeling techniques and for teaching residents and students by way of physicians, nurses, and other health care providers	The same as general pediatric care; primary care is what general pediatricians do in their practices most of the time and what general pediatricians in academia do part of the time
Sources for maintaining the clinical skills of the academic generalist	Ends in themselves; rather they are means to some other end, such as those listed to the left
Arenas for performing clinical research and paying attention to all subject needs and all research guidelines	Major sources of referrals to department subspecialists; such referrals come, primarily, from scores of practices in the area or region
Ways in which an institution (especially a state) can fulfill its social responsibility for providing health care to the medically underserved in the community	Sources of revenue for an academic department; the only way primary care can "pay for itself" is when the generalists do it 85% of the time, ie, in private practice.

cine, and inpatient care. They are also involved in the planning and implementation of continuing medical education after residency.

Developmental and Behavioral Pediatrics

The academic generalist is looked to by his/her subspecialist peers, school personnel, service agencies, and private practitioners for knowledge and skills to help resolve or handle developmental and behavioral issues affecting children they serve. Those of us with ready access to pediatric psychologists in our departments are most fortunate. A strong allegiance forms between these two disciplines in meeting the expectations of one's colleagues, the needs of children, and our responsibility within our department.

Preventive Pediatrics and Epidemiology

Increasingly, the general academic pediatrician is expected to have a good understanding of and skills in the implementation of preventive approaches using epidemiologic methods. These approaches range from infectious disease control in a day-care center to injury prevention in a "Pop Warner" football program to examining the devastating consequences of child abuse and violence in the family.

Community Services and Child Advocacy

The general academic pediatrician is expected to be involved in meeting the needs of children in the community. This may vary greatly from political advocacy to direct involvement in school activities, service programs for children, Head Start, sports activities, and migrant programs.

Administrative Responsibilities

There are two forms of administrative responsibilities that general academic pediatricians are asked to assume. First, those that we are *expected* to integrate into other responsibilities in the department or college (eg, the coordination of ambulatory facilities, involvment in teaching programs and newborn nurseries, and roles on college committees). Some of these functions, such as coordinating a course, may require a significant expenditure of time for a finite period. Second, administrative responsibilities that consume large amounts of time and significantly limit the other activities of a general academic pediatrician (eg, becoming an associate dean or director of pediatric residency or of a large ambulatory service). When this occurs, the assignments and functions in general academic pediatrics are limited to those related to this specific and finite activity. Such assigments are not appropriate functions for junior faculty trying to progress in academia.

Clinical Services

Primary Care.—Defined as "first contact, ongoing comprehensive health care," this role is similar, in most respects, to that of the general pediatrician in private practice, although the academic generalist spends significantly less time in this activity and usually cares for a much higher percentage of children receiving Medicaid. This is feasible, and even expected, because our salaries are, to a variable extent, derived from sources other than patient care. As indicated earlier, great confusion remains as to the purpose of primary care in an academic institution (Table).

Secondary Care.—This is defined as "periodic review and coordination of comprehensive health care services for children with complex, often chronic, problems." General pediatricians in an academic setting have the added responsibility of providing care to children with special pediatric, social, behavioral, and developmental problems. Examples include child abuse and neglect, sexual exploitation, attention deficit hyperactivity disorder, learning disabilities, major rearing problems, and medical problems that often stem from chronic multisystem diseases. While these problems may not fall under the purview of what is currently referred to as subspecialty pediatrics, several of the applicable subdisciplines require extensive training and knowledge as well as skills of sufficient magnitude to justify a special classification. Secondary care is commonly provided in the ambulatory setting, although fulfilling the needs of the inpatient child with multisystem disease is also the generalist's role. While pediatricians in private practice may have been trained for and are qualified to provide secondary care, and often do, the time required to handle the many problems of these children and their families prohibit the inclusion of a large number of such children in a fee-for-service setting (Table). Tertiary care pediatricians, on the other hand, commonly provide secondary care to their patients. The function of the academic generalists and subspecialists are not dissimilar in this regard.

Newborn Care.—With the advent and increased technologic sophistication of neonatology, the care of the newly born nonintensively ill infant has been given minimal attention as a specific academic entity. General pediatricians and family physicians perform physical examinations on admission and at discharge and check in with parents and nurses during the 24 to 48 hours permitted by the regulations of diagnosis related groups Practicing and academic general pediatricians have recently begun to realize this somewhat perfunctory care is insufficient.

Residents at our institution are being assigned to neonatal intensive care units for 4 to 6 months in contrast to 1 month in the nursery; neonatologists are becoming engulfed in technology and the care of a relatively small number of intensively ill newborns. Fewer women are receiving perinatal care, and many are single and have minimal social support. We now realize that many babies in the "term" or "well baby" nursery are neither well nor the product of a full-term pregnancy.

Cocaine, alcohol, herpes, acquired immunodeficiency syndrome, chlamydia, poverty, and abuse in childhood are all taking their toll; rarely do any of the newborns affected by these conditions require transfer to the intensive care unit. The words *term infant* and *well baby* no longer are appropriate for these newborns. As one of my colleagues apply stated, "This is the 'almost well' nursery." The role of the general pediatrician in caring for the newborn clearly has changed. Our task is to determine which baby is affected by these prenatal insults and what to do about it, all in 48 hours or less.

The challenge for the academic generalist is now becoming apparent. We must determine better ways to diagnose and care for these babies and their families and teach our residents to do likewise. This is a mission that hospital and academic administrators and third-party payors are only now *beginning* to recognize. Furthermore, how can an academic department of pediatrics provide primary care services to large numbers of medically indigent children and still expect its general pediatricians to be academicians?

Research

This function is listed last not because it is the least important, but rather to emphasize that research must encompass all of the previously listed functions of a general pediatrician in an academic department. In each of the previous six areas of responsibility, an ever-present, high degree of academic inquiry is necessary. Such inquiry often requires a basic understanding of clinical epidemiologic principles. The research must result in scientifically based information that can be transferred to others, not only by way of publication, but also by way of other peer-reviewed presentations, such as those incorporated into television programs, interactive computer programs, and other audiovisual aids.

The question of balance between the seven functions of the academic generalist, both in time and emphasis, must be ever present in the minds of academic administrators who delegate these responsibilities. While no specific percentage breakdown is feasible, or even desirable, each of the seven areas is integrated into the overall responsibilities of the general academic pediatrician. None should be eliminated, overemphasized, or underemphasized.

General pediatrics in an academic department of pediatrics is a broadly based discipline or "specialty." Primary care is but one of the clinical service responsibilities of the general pediatrician and is clearly not an end in itself. Increasingly, general pediatrics, as well as subspecialty services, are being provided on an ambulatory basis. Newborn medicine is an additional area of challenge and responsibility for the general pediatrician in an academic department.

COMMENT

In a 1991 newsletter from the Ambulatory Pediatric Association, Kathleen Nelson, president, raised some interesting questions about the future of the academic generalist.[5] She wondered if the advent of many more subspecialty boards will "mean the death of the generalist or more opportunities?" She also raised the important question of reimbursement. Will the diagnosis of otitis media cost more if made by a board-certified pediatric emergency subspecialist than by a board-certified generalist? These are important issues to which Dr Nelson invited our response.

While few academic generalists seem to be short of things to do in their respective departments, defining very clearly what we *do* accomplish is essential.

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Article

Safety and Immunogenicity of High-Dose Edmonston-Zagreb Measles Vaccine in Children With HIV-1 Infection

A Cohort Study in Kigali, Rwanda

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• ***Objective.***—To compare the reactogenicity and immunogenicity of high-dose Edmonston-Zagreb (EZ) measles vaccine in children with and without human immunodeficiency virus, type 1 (HIV-1), infection.

Design.—Prospective cohort study.

Setting.—General pediatric clinic and home visits in Kigali, the capital of Rwanda.

Participants.—Infants born to HIV-1–seropositive and –seronegative mothers were vaccinated with a $10^{5.0}$ 50% tissue culture infective dose of EZ measles vaccine at 6 months of age. Control visits were made 10 and 14 days later to monitor local and general reactions. Measles serum antibodies were measured by an enzyme-linked immunosorbent assay technique at birth and at 6 and 9 months of age. Three groups were compared: infected children (n=43), uninfected children born to seropositive mothers (n=135), and uninfected children born to seronegative mothers (n=194).

Results.—Three hundred twenty-three children (86.8%) were available for the reactogenicity study. No statistically significant difference between the three groups was found in the occurrence of minor adverse reactions. No severe adverse reaction was observed. One hundred ninety children (51.1%) were available for the immunogenicity study. The percentage of infants negative for measles antibody at 6 months was significantly higher ($P=.021$) in HIV-infected children (85%) and in uninfected children born to seropositive mothers (90%) than in uninfected children born to seronegative mothers (75%). The overall seroconversion rate at 9 months was 90% (95% confidence interval, 85.7% to 94.3%), without any statistically significant difference between the three groups.

Conclusion.—High-dose EZ vaccine administered at 6 months of age is safe and highly immunogenic in both HIV-infected and uninfected children.

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Despite the existence of an effective vaccine, measles remains a major public health problem in many developing countries.[1] The fatality rate associated with measles is particularly high in children below 1 year of age, making immunization early in life desirable.[2,3] The Edmonston-Zagreb (EZ) vaccine is a measles vaccine derived from the Edmonston-B virus strain after attenuation by passage in human diploid cells.[4] Recent studies carried out in different countries provide strong evidence that medium- and high-dose EZ vaccines are well tolerated and protective against measles among infants as young as 4 to 6 months of age.[5-9] This vaccine is in the process of being incorporated in the Expanded Programme on Immunization, particularly in areas where measles is a major cause of mortality before 9 months of age.[10]

In African pediatric populations, infection with the human immunodeficiency virus, type 1 (HIV-1), has also recently emerged as a major health problem.[11,12] It is now recognized that measles is particularly severe in children infected with HIV.[13-15] The World Health Organization (WHO)[16] and the Centers for Disease Control[17] both recommend that all HIV-infected children be vaccinated against measles, regardless of the stage of HIV disease. However, only scarce data are available so far on the reactogenicity and immunogenicity of measles vaccine in HIV-infected children.[15,18-21] In a prospective study in Zaire, Oxtoby et al[20] found that the rate of seroconversion after vaccination with Schwarz vaccine at 9 months of age was 89% in uninfected infants born to HIV-1–positive mothers vs 76% in asymptomatic infected infants.

The aim of the present study was to evaluate, in a comparative and prospective design, the safety and immunogenicity of high-dose EZ vaccine among infants aged 6 months with and without HIV-1 infection in Kigali, Rwanda.

SUBJECTS AND METHODS

Study Population

This study is part of a prospective cohort study carried out in Kigali on the mother-to-fetus/infant transmission of HIV-1 infection and on the natural history of HIV-1 infection in children from birth to 3 years of age. Methodological details of this prospective study are described elsewhere.[22] Briefly, after obtaining verbal consent from the mothers, 218 infants born to HIV-1–seropositive mothers were enrolled from November 1988 through June 1989 at the maternity ward of the Centre Hospitalier de Kigali (CHK), the only large hospital in Kigali, the capital of Rwanda, Central Africa. These 218 newborns were matched with 218 infants born to HIV-1–seronegative mothers of the same age and parity. Regular clinical, serological, and immunological follow-up is scheduled to 36 months of age. This study was approved by the Ministry of Health of Rwanda.

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Schedule of EZ Vaccination and Surveillance

High-dose EZ vaccine was systematically administered to 6-month-old children. The EZ vaccine used (batch EZ5D42) contained $10^{5.0}$ 50% tissue culture infective doses ($TCID_{50}$) of measles virus. The concentrated bulk was prepared by the Institute of Immunology of Zagreb, Yugoslavia, and the final vaccine was formulated and freeze-dried by SmithKline Beecham Biologicals, Rixensart, Belgium. Measles vaccine titrations were performed by SmithKline Beecham Biologicals using two internal references for each test. These references are regularly controlled in comparison with international references of the National Institute for Biological Standard and Control (Potters Bar, United Kingdom). Unused samples of vaccine were retitrated on completion of the program to confirm vaccine potency. Titers of unused vaccines varied from $10^{4.6}$ to $10^{4.9}$ $TCID_{50}$.

Children were visited at home by social workers 10 and 14 days after immunization to interview the mothers on the adverse events they had noticed following vaccination; the social workers also recorded on precoded files local and general adverse events they observed at the time of the visit. The social workers did not know the HIV serological status of the children. Beyond this initial 2-week period, the children were followed up every 15 days until 24 months of age either at CHK or at home. Children were referred to the study physicians if necessary. Measles was defined on clinical grounds using the case definition of the Centers for Disease Control.[23]

Biological Assays

Serum samples of the children were screened for HIV-1 antibodies at birth and every 3 months by a commercial enzyme immunoassay (Vironostika, Organon Teknika, Boxtel, the Netherlands). Serum samples positive by enzyme immunoassay were further confirmed by a commercial Western blot technique (du Pont de Nemours & Co, Wilmington, Del). A positive confirmation test was defined by the presence of at least one reactive band to an HIV-1 core protein (p17, p24, or p55) plus at least one reactive band to an HIV-1 envelope protein (gp41, gp120, or gp160).[24]

Mononuclear cell subpopulations were quantitated in children at the moment of measles vaccination using an indirect immunofluorescence technique and monoclonal antibodies: OKT4 for helper-inducer T cells ($CD4^+$) and OKT8 for suppressor-cytotoxic T cells ($CD8^+$) (Ortho Diagnostic Systems Inc, Raritan, NJ). A CD4/CD8 ratio of less than 1.0 was considered the criterion for impaired cellular immunity.[25]

Measles serum antibodies were assessed at birth and when the child was 3, 6, and 9 months old using a commercial enzyme-linked immunosorbent assay (Enzygnost, Behring Diagnostics, Marburg, Germany). Briefly, the WHO standard (international standard for antimeasles serum, first international standard preparation, 10 IU) was included in each test. The WHO standard, control, and study samples were serially diluted. The differences in absorbance were calculated at each dilution. A positive reaction was revealed by a difference in absorbance (study sample absorbance minus control absorbance $\geqslant 0.2$). The titers of the control and study samples were calculated against the WHO standard in milli–International Units per milliliter of serum by the four-parameter method.[26] The positive values of differences in absorbance ($\geqslant 0.2$) obtained for each dilution of the study samples were converted into milli–International Units per milliliter. The mean concentration of each sample was then calculated and expressed in milli–International Units per milliliter. Seroconversion following EZ vaccination was defined differently in children who did and did not lose their maternal measles antibodies prior to vaccination. The seroconversion rate following EZ vaccination of initially seronegative children (titers <32 mIU/mL) was defined as the detection of measles antibodies at 9 months of age. In initially seropositive infants, the response to vaccination was analyzed, taking into account the decline of maternally acquired measles antibodies between the ages of 6 and 9 months. Thus, the theoretical antibody titer the child would have reached at 9 months of age (T_tM9) if he or she had not been immunized at 6 months of age is:

$$T_tM9 = T_oM6/[2^{(M9-M6)/HL}],$$

where T_oM6 is the measles antibody titer observed at 6 months of age, M9 − M6 is the interval in days between the blood sample taken after vaccination (9 months of age) and the blood sample taken at the time of vaccination (6 months of age), and HL is the mean half-life of maternally acquired measles antibodies. The decrease in maternally acquired antibodies was calculated based on titration of serum samples of 140 infants (78 born to HIV-1–infected mothers and 62 born to uninfected mothers) who had serum samples available at birth and at 3 and 6 months of age. In this cohort, the mean half-life was approximately 30 days, assuming log-linear decrease of the antibody titers (data not shown). Nine children with an increase in titer between birth and 3 months or between 3 and 6 months of age were eliminated from the analysis to exclude subclinical measles infection. A child seropositive for measles antibodies at age 6 months was considered a seroconverter if the observed measles antibody titer at age 9 months was at least four times higher than the theoretical titer at 9 months.

Measles antibodies were also presented in terms of the proportion of children with titers of 200 mIU/mL or greater at age 9 months, since measles antibody concentrations lower than 200 mIU/mL after vaccination may not be protective.[27]

Classification of Children

After 15 months of follow-up, the children were divided into three groups:

Group 1 comprised HIV-1–infected children. HIV-1 infection in children was defined by the persistence of HIV-1 antibodies by Western blot assay at 15 months of age in children born to seropositive mothers. Those who died between 6 and 15 months of age were also classified as infected if they presented, during their last visit, with at least one major and one minor sign of the WHO clinical case definition for pediatric acquired immunodeficiency syndrome.[28] One modification was made to this definition: if present, severe and/or recurrent pulmonary infection was considered a major sign in the place of chronic cough as a minor sign.[29] In addition, six children born to seronegative mothers but who became HIV-1 seropositive at 6 months of age or younger were also considered infected for the present analysis and were included in group 1. Postnatal mother-to-child transmission through breast milk was implicated in these six children, because their mothers, who were retrospectively followed up, seroconverted to HIV-1 during this period, and other modes of contamination of the children (blood transfusions, medical injections, and skin piercing) were ruled out.[30]

Group 2 comprised uninfected children born to HIV-1–infected mothers. Children who were born to HIV-1–infected mothers but who were HIV-1 seronegative by Western blot assay at 15 months of age were considered uninfected.

Group 3 comprised uninfected children born to HIV-1–seronegative mothers.

Finally, children who were born to HIV-1–infected mothers and who died or were unavailable for follow-up without being classified in group 1 or 2 were excluded from this analysis.

Statistical Methods

Geometric mean measles antibody titers (GMTs) were computed. Results are reported according to the WHO guidelines for measles vaccine field trials.[31] Titers lower than 32 mIU/mL were excluded for the calculation of GMTs. Two-sided χ^2 test, Fisher's Exact Test, Student's t test, and variance analysis were used for comparisons when appropriate.

RESULTS

Follow-up of the Cohort and Measles Vaccination Schedule

Among the 436 newborns enrolled at birth in this cohort, 387 were immunized with the high-dose EZ vaccine (Table 1). There was no difference between children

Table 1.—Demographic Characteristics of HIV-1–Infected and Uninfected Children Immunized With High-Dose EZ Vaccine at 6 Months of Age, Kigali, Rwanda, 1989-1990*

	Group 1 (Infected Children)	Group 2 (Uninfected Children Born to HIV-1–Positive Mothers)	Group 3 (Uninfected Children Born to HIV-1–Negative Mothers)	Total
No. of children vaccinated	43	135	194	**372**
M/F ratio (No. of children)	0.79 (19/24)	1.11 (71/64)	0.88 (91/103)	0.95 (181/191)
Mean (median) age at vaccination, d	193 (188)	192 (188)	193 (187)	193 (188)
No. (%) followed up for adverse events	36 (84)	121 (90)	166 (86)	**323** (87)
No. (%) followed up for antibody at age 9 mo	20 (46)	83 (61)	87 (45)	**190** (51)

*HIV-1 indicates human immunodeficiency virus, type 1; EZ, Edmonston-Zagreb.

born to seropositive and seronegative mothers in the number unavailable for follow-up prior to vaccination (11 of 218 vs 12 of 218 cases). However, 17 children (8%) born to seropositive women had died before 6 months of age vs seven children (3%) born to seronegative mothers ($P = .036$, χ^2 test). Two measles cases were observed before the age of vaccination in children born to seropositive women. Altogether, the number of vaccinated children was 43 for group 1 (including five of the six children infected postnatally with HIV-1), 135 for group 2, and 194 for group 3; the 15 children who could not be classified into any group were also vaccinated. The median age at EZ vaccination was 188 days (range, 177 to 309 days), and the mean age was 193 days (SD, 16 days), without any statistically significant difference between the groups (Table 1). The overall proportion of children vaccinated between 25 and 28 weeks was 81.2%. No other vaccine was administered concomitantly with EZ immunization.

Reactogenicity

We studied adverse events following EZ immunization among those children vaccinated between 25 and 32 weeks of age whose first control visit was between 8 and 14 days after vaccination. The number of children fulfilling these criteria was 36 in group 1 (84%), 121 in group 2 (90%), and 166 in group 3 (86%) (Table 1). Among these 323 infants, 178 (55%) had two control visits and 145 (45%) had one visit during the initial 2-week period.

Table 2 includes data from the mothers' interviews and on signs and symptoms observed by the social workers in these 323 children. No statistically significant difference in the occurrence of adverse events after EZ vaccination was observed between the three groups of children, either from the mothers' interviews or from the signs and symptoms observed by the social workers ($P > .1$ for all comparisons between the three groups). One child from group 2 presented with febrile seizures 3 days after vaccination. No other severe adverse reaction to EZ vaccination, such as atypical pneumonia or encephalitis, was noticed during follow-up. Three children with full-blown acquired immunodeficiency syndrome and five children with at least one major and one minor sign of the WHO case definition of pediatric acquired immunodeficiency syndrome were immunized without adverse events.

Immunogenicity

Four children of the cohort died between 6 and 9 months of age, and five were unavailable for follow-up. Among the 372 children vaccinated with the EZ strain, 190 (51.1%) had serum samples available at 6 and 9 months of age for determination of measles antibody titers (Table 1). Their median age at vaccination was 186.5 days (range, 178 to 230 days), and 157 (82.6%) of them were vaccinated between 25 and 28 weeks of age. These 190 children available for the immunogenicity study were comparable to the 182 others in the proportion with a reversed CD4/CD8 ratio at 6 months of age. The proportion of children with test results negative for measles antibodies at 6 months of age differed significantly ($P = .021$) between the three groups (Table 3). This proportion was not different between groups 1 and 2 ($P = .44$, Fisher's Exact Test). When grouping the results of the 101 children born to HIV-1–positive mothers, 11 (11%), had detectable measles antibodies by enzyme-linked immunosorbent assay at 6 months of age vs 22 (25%) of 89 infants born to HIV-1–negative mothers ($P = .001$, χ^2 test).

The overall rate of response following EZ vaccination, evaluated when the children were 9 months old, was 90% (95% confidence interval [CI], 85.7% to 94.3%, Table 4). The seroconversion rate to measles immunization was not statistically different between the three groups of subjects studied. The GMT of measles antibodies at 9 months of age was also comparable in the three groups of children. The proportion of children with measles antibody levels of 200 mIU/mL or greater was not statistically different when comparing the three groups. When the analysis was restricted to children vaccinated between 25 and 28 weeks of age, the overall seroconversion rate was 89% (140 of 157 children; 95% CI, 84.3% to 94.0%) without any difference between the three groups. The two symptomatic children from group 1 who had serum samples available at 6 and 9 months of age had responses.

The response to the EZ vaccine was dependent on prevaccination antibody status. Infants seronegative for measles antibodies at age 6 months had lower titers at birth (GMT, 2544 mIU/mL; range, 55 to 17 264 mIU/mL; $n = 121$) than those seropositive at age 6 months (GMT, 5923 mIU/mL; range, 148 to 30 198 mIU/mL; $n = 27$) ($P < .001$, Student's t test). The seroconversion rate of infants seronegative at 6 months was 96% (151 of 157 children; 95% CI, 93.2% to 99.2%), with no statistically significant difference between the three groups (group 1, 15 [88%] of 17 children; group 2, 72 [96%] of 75 children; group 3, 64 [98%] of 65 children; $P = .15$, χ^2 test). Among the children with measles antibodies at age 6 months, the overall seroconversion rate was 61% (20 of 33 children; 95% CI, 43.9% to 77.3%). Therefore, lack of response to EZ vaccine was more frequent in children with measles antibodies at age 6 months

Table 2.—Reactogenicity of High-Dose EZ Vaccine Given at 6 Months of Age to HIV-1–Infected and Uninfected Children, Kigali, Rwanda, 1989-1990*

	Reactogenicity, No. (%)			
	Group 1 (Infected Children) (n=36)	Group 2 (Uninfected Children Born to HIV-1–Positive Mothers) (n=121)	Group 3 (Uninfected Children Born to HIV-1–Negative Mothers) (n=166)	P†
Mother's interview				
Local reaction	2 (6)	6 (5)	12 (7)	.72
Perceived fever	12 (33)	28 (23)	30 (18)	.12
Skin eruption	2 (6)	12 (10)	20 (12)	.49
Upper respiratory tract infection	9 (26)	29 (24)	28 (17)	.24
Cough	9 (26)	26 (21)	25 (15)	.22
Clinical examination by social worker				
Local reaction	1 (3)	3 (2)	4 (2)	.99
Rectal temperature>38.5° C	0	1 (1)	2 (1)	.77
Skin eruption	4 (11)	12 (10)	13 (8)	.74
Upper respiratory tract infection	6 (17)	29 (24)	24 (14)	.12
Cough	9 (26)	26 (21)	25 (15)	.20

*HIV-1 indicates human immunodeficiency virus, type 1; EZ, Edmonston-Zagreb.
†χ^2 test, *df*=2.

Table 3.—Measles Antibody Titers at 6 Months of Age in HIV-1–Infected and Uninfected Children, Kigali, Rwanda, 1989-1990*

	Group 1 (Infected Children) (n=20)	Group 2 (Uninfected Children Born to HIV-1–Positive Mothers) (n=83)	Group 3 (Uninfected Children Born to HIV-1–Negative Mothers) (n=87)	Total (n=190)	P
No. (%) of children with detectable measles antibodies at 6 months of age	3 (15)	8 (10)	22 (25)	33 (17)	.021†
GMT (range) of children with measles antibodies at 6 months of age, mIU/mL	273.6 (63-636)	82.3 (42-171)	163.5 (32-6568)	145.1 (32-6568)	.32‡

*HIV-1 indicates human immunodeficiency virus, type 1; GMT, geometric mean titer.
†χ^2 test, *df*=2.
‡Variance analysis.

Table 4.—Antibody Response at 9 Months of Age After Immunization With High-Dose EZ Vaccine at 6 Months of Age in HIV-1–Infected and Uninfected Children, Kigali, Rwanda, 1989-1990*

	Group 1 (Infected Children) (n=20)	Group 2 (Uninfected Children Born to HIV-1–Positive Mothers) (n=83)	Group 3 (Uninfected Children Born to HIV-1–Negative Mothers) (n=87)	Total (n=190)	P
No. (%) of seroconverters at 9 months of age	18 (90)	78 (94)	75 (86)	171 (90)	.24†
GMT (range) of seroconverters at 9 months of age, mIU/mL	349.6 (43-5197)	270.7 (45-2232)	232.6 (32-3216)	260.2 (32-5197)	.26‡
No. (%) of seroconverters with GMT antibody level ≥200 mIU/mL at 9 months of age	15/20 (75)	58/83 (64)	45/87 (52)	113/190 (59)	.09†

*HIV-1 indicates human immunodeficiency virus, type 1; EZ, Edmonston-Zagreb; and GMT, geometric mean titer.
†χ^2 test, *df*=2.
‡Variance analysis.

(39%) than in children without measles antibodies at age 6 months (4%) ($P<.001$; relative risk, 10.3; 95% CI, 4.2 to 25.1). However, among the seroconverters, the GMT at age 9 months was comparable to that in children who had measles antibodies at age 6 months (407 mIU/mL; range, 46 to 3216 mIU/mL; n = 20) and to that in children who were seronegative at age 6 months (446 mIU/mL; range, 32 to 5197 mIU/mL; n=151) ($P=.80$, Student's *t* test). When stratified according to the presence or absence of measles antibodies at age 6 months, the responses of groups 1 and 3 were not statistically different ($P=.68$, adjusted Mantel-Haenszel χ^2 analysis).

The CD4 and CD8 lymphocyte counts were performed for 159 (84%) of the 190 children included in the analysis of immunogenicity. The overall seroconversion rate at age 9 months in this subset was 90%. The proportion of chil-

Table 5.—Antibody Response at 9 Months of Age After Immunization at 6 months of Age in HIV-1–Infected and Uninfected Children According to CD4/CD8 Ratio at Vaccination, Kigali, Rwanda, 1989-1990*

	Group 1 (Infected Children)	Group 2 (Uninfected Children Born to HIV-1–Positive Mothers)	Group 3 (Uninfected Children Born to HIV-1–Negative Mothers)	Total
CD4/CD8 ratio ≥1				
No. of children	7	57	65	129
No (%) of responders	7 (100)	53 (93)	58 (89)	118 (91)
GMT (range), mIU/mL	469.8 (113-5197)	256.8 (45-975)	231.8 (32-3216)	253.1 (32-5197)
CD4/CD8 ratio <1				
No. of children	9	14	7	30
No. (%) of responders	8 (89)	13 (93)	4 (57)	25 (83)
GMT (range), mIU/mL	230.2 (43-517)	264.6 (51-1390)	318.2 (32-2280)	260.6 (32-2280)
Total				
No. of children	16	71	72	159
No. (%) of responders	15 (94)	66 (93)	62 (86)	143 (89)
GMT (range), mIU/mL	321.2 (43-5197)	258.3 (45-1390)	236.6 (32-3216)	254.4 (32-5197)

*HIV-1 indicates human immunodeficiency virus, type 1; GMT, geometric mean titer. No comparisons between strata and between groups were statistically significant.

dren with a reversed CD4/CD8 ratio was 56% in group 1 (nine of 16 children), 20% in group 2 (14 of 71 children), and 10% in group 3 (seven of 72 children) ($P=.001$, χ^2 test, $df=2$) (group 2 vs group 3: $P=.09$, χ^2 test, $df=1$). Group 1 children with a reversed CD4/CD8 ratio had a response rate of 89% (eight of nine children, Table 5). No statistically significant difference in seroconversion at 9 months of age was manifest when the three groups of children were stratified according to their CD4/CD8 ratio at 6 months of age (group 1 vs group 3: $P=.22$, adjusted Mantel-Haenszel χ^2 analysis).

After a follow-up ranging from 13 to 19 months after EZ vaccination, none of the children in the cohort had presented clinical measles, despite frequent accidental exposure during routine visits at CHK. Indeed, during the 2-year period 1989 and 1990, 213 children with measles were hospitalized in the pediatric ward of CHK (median age, 18 months; range, 4 months to 13 years). Eight of them (4%) were below 6 months of age, and 35 (17%) were between 6 and 8 months of age. Finally, none of the deaths that occurred in the cohort between vaccination and December 1990 (15 in group 1, one in group 2, and one in group 3) were temporally related to immunization with EZ vaccine.

COMMENT

The EZ vaccine used in this study presents advantages for immunization strategies in developing countries over other antimeasles strains, such as the currently used Schwarz vaccine. Indeed, it has been proven safe and effective in children as young as 4 months of age.[5-8] Therefore, it could stimulate an immune response in most infants before they lose maternally acquired measles antibodies. In a recent study carried out in Mexico,[9] high and medium doses of EZ vaccine were more immunogenic in 6-month-old infants than the Schwarz vaccine at 9 months of age. In the context of pediatric HIV-1 infection, vaccinating infants against measles earlier than 9 months of age offers additional advantages. First, these subjects could benefit from immunization prior to the development of severe immunodeficiency. Prospective cohort studies on the perinatal transmission of HIV-1 infection emphasize the early occurrence of severe HIV-related disease in African children.[32-34] Second, infants born to HIV-1–infected mothers, whether themselves infected or not, may lose their maternal measles antibodies earlier than children of HIV-1–seronegative women. In the present study, approximately 90% of the infants born to HIV-1–infected mothers had lost their measles antibodies at 6 months of age. As an expected consequence of this rapid loss of maternal measles antibodies, two cases of measles diagnosed before 6 months of age in our cohort both occurred in infants of HIV-1–infected mothers. The reason why children of HIV-1–seropositive mothers become seronegative to measles antibodies earlier than the others remains unknown. In the present series, the GMT of measles antibodies at birth was not different between infants born to HIV-1–seropositive mothers (1923.4 mIU/mL; range, 111 to 30 198 mIU/mL; n=95) and infants born to HIV-1–seronegative women (1634.4 mIU/mL; range, 55 to 32 767; n=82) ($P=.36$, Student's t test). However, recent studies in Africa have shown comparable low rates of measles antibodies carriage at 6 months of age, regardless of the HIV status of the children.[8,35]

In spite of vaccine virus titers up to 100-fold greater than the standard dose, the present study was not able to demonstrate that HIV-1–infected children present higher rates of adverse clinical reactions than uninfected children in the 2 weeks following EZ immunization. High fever was rare; atypical pneumonia and encephalitis were not observed. Although larger series of HIV-infected children followed up for a longer period of time are required before definitive conclusions can be drawn, especially for rare serious outcomes, such as encephalitis, these findings have important public health implications and reinforce recommendations of the WHO[16] and the Centers for Disease Control[17] that all HIV-infected children should be vaccinated against measles.

We confirm that infants not infected by HIV-1 have high seroconversion rates following immunization with high-dose EZ vaccine at 6 months of age.[5-9] Furthermore, although the numbers of HIV-infected children studied were small, immunization with EZ vaccine induced the production of measles antibodies in HIV-1–infected children in a proportion similar to that observed in uninfected subjects. However, in a cohort study of children immunized at 6 months of age with high-dose EZ vaccine in Zaire, HIV-infected infants had a lower seroconversion rate than uninfected children.[21] In the present study, even HIV-infected infants with cell-mediated immune dysfunction had a high seroconversion rate after EZ immunization. This finding is particularly important when considering that infants born to HIV-infected mothers seem to lose their antibodies more rapidly than others and could therefore be at greater and earlier risk of acquiring measles infection. None of the children of the cohort presented with measles disease following vaccination. Krasinski and Borkowksy[15] recently described measles in two of six HIV-infected children who had detectable measles antibodies following vaccination. Moreover, it appears that the antibody response measured by enzyme-linked immunosorbent assay 3 to 6 months after measles vaccination correlates poorly with the persistence of antibodies at 24 months of age.[36] Longer follow-up of our cohort of HIV-1–infected and uninfected children is therefore planned to determine the duration of measles antibody persistence and the long-term clinical efficacy induced by high-dose EZ vaccine given at 6 months of age, as has already been done elsewhere for healthy children.[36-38]

The recommended practice of integrating EZ vaccine at 6 months of age to the schedule of the Expanded Programme on Immunization should be continued in Africa and in other parts of the world, regardless of the HIV serostatus of the children.

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Clinical Reactions and Immunogenicity of the BIKEN Acellular Diphtheria and Tetanus Toxoids and Pertussis Vaccine in 4- Through 6-Year-Old US Children

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• *Objective.*—To compare the immunogenicity and reactogenicity of a two-component acellular pertussis vaccine with a whole-cell diphtheria and tetanus toxoids and pertussis vaccine (W-DTP) when administered as a booster to children 4 through 6 years of age.

***Design.*—This was a randomized, double-blind study.**

***Setting.*—Children in this study were from three general pediatric practices (two were private, one was university-affiliated).**

***Participants.*—Three hundred and sixteen 4- through 6-year-old children who had received four previous W-DTP immunizations at the recommended times were studied.**

***Selection Procedures and Interventions.*—Children were randomly assigned in a 1:3 ratio to receive either W-DTP or one of three lots of acellular diphtheria and tetanus toxoids and pertussis vaccine (A-DTP). The A-DTPs contained 3.75 μg each of lymphocytosis promoting factor and filamentous hemagglutinin protein nitrogen per 0.5 mL and the same concentrations of diphtheria and tetanus toxoids as W-DTP. Serum samples were obtained on the day of immunization and 4 to 6 weeks later. Adverse reactions were recorded by parents at 6, 24, 48, and 72 hours.**

***Measurements and Results.*—An indirect enzyme-linked immunosorbent assay (ELISA) method determined IgG antibody response to lymphocytosis promoting factor, filamentous hemagglutinin, and tetanus toxoid; a CHO cell assay measured neutralizing antibodies to pertussis toxin; and serum neutralization on VERO cells assayed diphtheria antitoxin. One month after booster doses were administered, the geometric mean antibody levels for A-DTP vs W-DTP were IgG filamentous hemagglutinin, 408 vs 81 ELISA U/mL; IgG lymphocytosis promoting factor, 362 vs 104 ELISA U/mL; CHO cell, 210 vs 107; diphtheria, 21.7 vs 12.1 U/mL;, and tetanus, 2.86 vs 2.04 Eq/mL. Following immunization with A-DTP, local and systemic adverse experiences were 30% to 50% and 20% to 30% fewer, respectively, as compared with W-DTP.**

***Conclusions.*—The BIKEN A-DTP vaccine used in this study demonstrates enhanced immunogenicity to lymphocytosis promoting factor, filamentous hemagglutinin, and other measured antigens and less reactogenicity compared with licensed W-DTP.**

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Although whole-cell diphtheria and tetanus toxoids and pertussis vaccine (W-DTP) is effective in the prevention of whooping cough,[1] concern for adverse reactions that are temporally related to the pertussis vaccine has prompted extensive review[2-6] and increased litigation[7] and cost. These issues have been a major impetus for the development of a diphtheria and tetanus toxoids and parents at 6, 24, 48, and 72 hours. Pertussis vaccine (DTP) that contains a less reactogenic pertussis component. Whether a causal relationship exists between whole-cell pertussis vaccination and permanent neurologic sequelae has been seriously questioned.[8-13]

Nevertheless, the high rate of common local and systemic events associated with the administration of W-DTP[14-16] justifies the continued development of less reactogenic acellular DTP vaccines.

The purpose of our study was to evaluate the immunogenicity and reactogenicity of a two-component acellular pertussis vaccine as compared with W-DTP when administered as a booster to children 4 through 6 years of age.

METHODS

Subject Selection

Healthy children from three study sites (Rochester, NY, Sellersville, Pa, and Pittsburgh, Pa) were eligible to participate if they had no personal or family history of developmental delay or neurologic disorder and had received four previous W-DTP immunizations at the usual recommended times. Subjects were excluded if they had previously received an acellular pertussis vaccine or if they had a reaction to a previous W-DTP that contraindicated (as defined by the American Academy of Pediatrics Red Book Committee) further immunization with pertussis vaccine. No vaccination was given within 7 days of a febrile illness. The study received Institutional Review Board approval at each study site, and parental written informed consent was obtained prior to enrollment.

Vaccines

The W-DTP used in this study was the commercially available vaccine (Lot 9J01114) produced by Connaught Laboratories (Swiftwater, Pa) and contained 6.7 flocculating units (LfU) of

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Table 1.—Percentage of Children Who Experienced Local Reactions Within 72 Hours of Immunization With A-DTP or W-DTP*

Reaction	A-DTP† (n=240)	W-DTP (n=76)	*P*
Tenderness	46.2	93.4	<.0001
Erythema	31.3	60.5	<.0001
Erythema >2.5 cm	17.9	47.4	<.0001
Swelling	27.9	59.2	<.0001
Any reaction	57.9	94.7	<.0001

*A-DTP indicates acellular diphtheria tetanus toxoids and pertussis vaccine; W-DTP, whole-cell diphtheria tetanus toxoids and pertussis vaccine.

†Indicates pooled lots.

Table 2.—Percentage of Children Who Experienced Systemic Reactions Within 72 Hours of Immunization With A-DTP or W-DTP*

Reaction	A-DTP† (n=240)	W-DTP (n=76)	*P*
Temperature >38°C	4.3	18.2	.0006
Irritability	15.8	44.7	<.0001
Drowsiness	15.0	32.9	.0007
Anorexia	5.4	25.0	<.0001

*A-DTP indicates acellular diphtheria tetanus toxoids and pertussis vaccine; W-DTP, whole-cell diphtheria tetanus toxoids and pertussis vaccine.

†Indicates pooled lots.

diphtheria toxoid, 5 LfU of tetanus toxoid, and 5 protein nitrogen units of pertussis antigen per 0.5 mL dose. The acellular pertussis components were produced by the Kanonji Institute, the Research Foundation for Microbiological Diseases (BIKEN) of Osaka University, Japan. Acellular diphtheria and tetanus toxoids and pertussis vaccine (A-DTP) (IND lots 4547, 4548, and 4549) was formulated at Connaught Laboratories by combining the acellular components with diphtheria and tetanus toxoids. The final concentration for each antigen (lymphocytosis promoting factor [LPF] and filamentous hemagglutinin [FHA]) was 3.75 μg protein nitrogen per 0.5 mL. Diphtheria and tetanus toxoid concentrations were the same as in the W-DTP. Both vaccines were adsorbed onto the same amount of aluminum potassium sulfate (0.1 mg/0.5 mL) and had the same amount (0.01%) of thimerosal added as a preservative. The same lots of vaccine were used at each study site.

Study Design

At each study site, children were randomly assigned in a 1:3 ratio using double-blind design to receive either W-DTP or one of the three lots of A-DTP. The vaccine was given as an intramuscular injection in the deltoid region. A 25-gauge 5/8-in needle was used and it was neither changed nor wiped before injection. No air was injected prior to its removal from the muscle. The children were observed for 15 minutes for any immediate adverse event. Local reactions (tenderness, erythema, severe erythema of greater than 2.5 cm, and swelling) were observed by parents and recorded on a standard form 6, 24, 48, and 72 hours after immunization. Systemic events (irritability, drowsiness, anorexia, vomiting, temperature of greater than 38°C, diarrhea, and persistent or unusual crying) were noted and recorded at 6, 24, 48, and 72 hours. The observation period was extended to 14 days for any adverse experiences that were not resolved by 72 hours or that occurred after 72 hours. Analgesics were not routinely given. Parents were telephoned by a nurse from the study 1, 3, and 14 days after immunization, at which time adverse experiences were reviewed and documented on a standardized form. An interval history was obtained 4 to 6 weeks after immunization.

Serologic Assays

Blood was obtained by venipuncture the day of immunization and 4 to 6 weeks later. Serum samples were separated and frozen at −20°C until assayed at Connaught Laboratories. An indirect enzyme-linked immunosorbent assay method was used to determine the IgG antibody response to LPF, FHA, and tetanus toxoid.[17] Neutralizing antibodies to pertussis toxin were measured by a CHO cell assay.[18] Diphtheria antitoxin was assayed by serum neutralization on VERO cells.[19]

Statistical Analysis

All statistical analyses were performed on a specialized computer program (Statistical Application System version 6.04, SAS Institute Inc, Cary NC). Demographic characteristics among the four randomized groups were carefully analyzed. Adverse experiences and immunologic responses were then compared with recipients of the acellular lots. Because lot differences were not significant, the lots were pooled and the combined data compared with the whole-cell vaccine. Adverse experiences were analyzed by logistic regression at each time as specified by the protocol. The occurrence of any adverse event at any time within 3 days of the administration of the vaccination was analyzed. Serologic data were analyzed only from children who had both preimmunization and postimmunization serum samples available for assay. A serologic response was defined as at least a fourfold increase in antibody levels. The percentage of children who responded to immunization were compared by logistic regression. Analysis of the geometric mean of prevaccination and postvaccination antibody levels were compared by analysis of variance on the log transformed raw data. The ratios of postvaccination to prevaccination geometric mean antibody levels were also analyzed. All analyses examined possible variation among study sites.

RESULTS

Demographics

Three hundred and sixteen children, 174 males and 142 females, were enrolled and all completed the study. The mean age was 57 months (range, 47 through 78 months). Eighty-two percent of the children were white. Although the mean ages and the racial distribution of study subjects were different at each site, there was no age or race difference between any vaccine group at individual study sites.

REACTOGENICITY

Local Adverse Reactions

The incidence of any local adverse reaction up to 72 hours following immunization in children who received W-DTP was significantly greater than in those who received A-DTP (Table 1). Although not shown in the table, tenderness, erythema, erythema of greater than 2.5 cm, and swelling occurred in a significantly greater proportion in those immunized with W-DTP ($P = .005$ to $< .0001$) at 24 and 48 hours after vaccination. Except for erythema, the frequency of each local reaction was at least doubled after W-DTP was administered as compared with the reaction after A-DTP was administered. This difference was most marked with tenderness at each recorded time and occurred two to three times more frequently in the group given W-DTP. Adverse local reactions reported in both the groups given A-DTP and W-DTP between 4 and 14 days after immunization were infrequent and showed no statistically significant or consistent differences.

Systemic Adverse Events

A temperature of greater than 38°C, irritability, drowsiness, and anorexia within 72 hours of immunization oc-

Table 3.—Geometric Mean (GM) Values, the Percentage of Children Who Responded With a Greater Than Fourfold Antibody Level Rise, and the Ratio of Post- to Pre-GM Values After Immunization at 4 Through 6 Years of Age With A-DTP (n=211) or W-DTP (n=65)*

	Pre-GM	Post-GM	>Fourfold Increase, %	Post-GM/Pre-GM†
Lymphocytosis promoting factor				
A-DTP	14.5	408	89.1	28.1
W-DTP	15.2	81	55.4	5.3
P	.7824	<.0001	<.0001	<.0001
Filamentous hemagglutinin				
A-DTP	18.9	362	87.2	19.2
W-DTP	19.2	104	55.4	5.4
P	.8377	<.0001	<.0001	<.0001
CHO cell				
A-DTP	23.6	210	69.7	8.9
W-DTP	27.9	107	50.8	3.8
P	.4056	.0194	.0072	.0001
Diphtheria				
A-DTP	0.46	21.7	99.5	47.5
W-DTP	0.48	12.1	93.8	25.2
P	.8002	.0001	.0196	.0005
Tetanus				
A-DTP	0.14	2.86	92.4	20.1
W-DTP	0.16	2.04	78.5	12.4
P	.2995	.0042	.0015	.0039

*A-DTP indicates acellular diphtheria tetanus toxoids and pertussis vaccine; W-DTP, whole-cell diphtheria tetanus toxoids and pertussis vaccine.

†Geometric mean values are measured in enzyme-linked immunosorbent assay units per milliliter for lymphocytosis promoting factor and filamentous hemagglutinin. Tetanus antitoxin is expressed as equivalents per milliliter. Serum neutralizing antibody for CHO is expressed as reciprocal of the titer. Diphtheria antitoxin is expressed as units per milliliter.

curred statistically more frequently in children following immunization with W-DTP compared with A-DTP (Table 2). These differences were most evident at 24 hours after administration and decreased thereafter. The incidence of a temperature of greater than 38.4°C was low (<5%) in both groups and was not statistically significant. The other systemic reactions (vomiting and diarrhea) were also reported in less than 5% of the children in either group. Hypotonic episodes, seizures, or high-pitched or persistent crying did not occur in any child in either group. There were no significant differences in the occurrence of intercurrent illnesses that might explain the differences in the observed rates of systemic events.

IMMUNOGENICITY

Antibody responses to the various vaccine components are presented in Table 3. Serological data were available from 87% of enrollees. The loss of blood samples during transportation to the laboratory or absent or insufficient serum samples that were required to complete laboratory analysis on both preimmunuzation and postimmunization serum samples accounted for those not included in analyses. Four to six weeks after immunization, antibody responses to FHA and LPF were 3.5 to five times greater, respectively, in those who received A-DTP. Postvaccination geometric mean pertussis neutralizing antibody, diphtheria antitoxin, and tetanus toxoid values were also significantly greater in the group with A-DTP.

The percentage of children who responded with at least a fourfold increase in LPF and FHA antibody levels was greater in the recipients of A-DTP—almost 90% compared with 55% in the group given W-DTP. The ratios of postvaccination to prevaccination geometric mean antibody levels were also greater in the acellular group.

No significant interaction effects between vaccine lots and study sites were observed for any reaction rates or serologic factors.

COMMENT

This study is the first US trial to compare the reactogenicity and immunogenicity of the Connaught/BIKEN two-component A-DTP with W-DTP as a booster dose in 4- through 6-year-old children. Local and systemic adverse reactions were 30% to 50% and 20% to 30% fewer, respectively, in the group given A-DTP. These results are consistent with other studies of the BIKEN-type vaccine.[20-24] In contrast to a previous report,[25] no local reactions were seen 7 to 10 days after vaccination.

Infants immunized with the BIKEN acellular vaccine responded with LPF and FHA antibody levels that were 2.5 and six times greater, respectively, than these values were in infants of similar ages who were recovering from pertussis.[26] In our study, the immune responses to these antigens following administration of A-DTP were five and 3.5 times greater than those observed following W-DTP, and more children responded with a fourfold or greater increase in antibody levels following immunization with A-DTP compared with W-DTP. Our results are consistent with previous studies that have demonstrated that acellular vaccines that contain LPF/FHA are highly immunogenic.[23,26,27] A serological correlation for clinical protection from pertussis has yet to be defined. As the whole-cell vaccine has been shown to be efficacious,[1] perhaps the high levels of LPF and FHA antibody as we documented are not necessary, and/or perhaps other antibodies such as to agglutinogens, to 69-kd outer membrane protein (which is contained in some other acellular pertussis vaccines), or to other antigens as yet to be identified, may play important roles in conferring protection.

Responses to diphtheria and tetanus toxoids were enhanced in the group given A-DTP compared with the group given W-DTP. The reason for this is uncertain, evidence suggests LPF may enhance the immune response.[28] However, according to the manufacturer, the BIKEN vaccine has shown minimal reversion to active LPF compared with other acellular pertussis vaccines used in Japan. Although the vaccines had identical concentrations of diphtheria and tetanus toxoids, different lots were used and they may have had subtly different antigenic compositions.

The W-DTP has been noted to have a clinical efficacy of 63% to 91%.[1] In Japan, where the BIKEN-type A-DTP vaccine has been one of several formulations used routinely in children aged 2 years and older since 1981, A-DTP vaccines have had efficacy rates of 77% to 98%, although none of these were in prospective, randomized, and controlled trials.[29-35] In the Swedish trial with an acellular vaccine that contained the same concentration of LPF and FHA as our study vaccine, efficacy (based on parental reporting) was 85%; protection against culture-confirmed pertussis, including any duration of cough, was estimated to be 69%.[36] Based on clinical symptoms, another study calculated the efficacy of BIKEN vaccine to be 89.4%, using a mathematical method of correcting the number of reported cases to the adjusted number of cases per population of 100 000.[37] These comparisons need to be interpreted with caution as case definitions, surveillance techniques, and the methods used to calculate vaccine efficacy varied. Differences in vaccine composition as well as the age of the vaccinees also may be important determinants of efficacy.[38]

Our study has shown that the Connaught/BIKEN A-DTP is less reactogenic and, with regard to the pertussis antigens it contains (LPF and FHA), is more immunogenic than W-DTP. Its immunogenicity to LPF and FHA is comparable with that of other A-DTP vaccines shown to be efficacious during a decade of use in Japan. Although studies with pertussis vaccines that contain different ratios of the same antigens and additional antigens are ongoing, superior efficacy of one type has not been demonstrated. It thus appears reasonable to consider licensure of BIKEN A-DTP for US children, at least for the 4- through 6 year-old booster dose.

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Severity and Frequency of Sequelae of Bacterial Meningitis in Alaska Native Infants

Correlation With a Scoring System for Severity of Sequelae

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• *Objectives.*—To (1) determine the frequency and severity of sequelae of *Haemophilus influenzae* type b and *Streptococcus pneumoniae* meningitis in Alaska Native children, (2) compare morbidity and mortality of *H influenzae* b and *S pneumoniae* meningitis, and (3) evaluate the applicability of the Herson-Todd prognostic score (HTPS) to both *H influenzae* b and *S pneumoniae* meningitis in this population.

Design.—A retrospective study of all cases of *H influenzae* b and *S pneumoniae* meningitis in Alaska Native children younger than age 5 years. Data on meningitis sequelae, obtained from medical charts and records of the Infant Learning Program, were collected, and incidence of sequelae tabulated. Data obtained on admission to the hospital were used to calculate HTPS.

Setting.—Indian Health Service facility for the Yukon-Kuskokwin Delta region of southwest Alaska.

Study Subjects.—51 of 63 Alaska Native children with *H influenzae* b meningitis and 13 of the same 63 Alaska Native children with *S pneumoniae* meningitis occurring between 1980 and 1988. One child was infected with both organisms, producing a total of 64 cases for study.

Selection Procedures.—Cases were identified by surveillance for these diseases between January 1, 1980, and December 31, 1988, maintained by the Arctic Investigations Program, Centers for Disease Control.

Measurements and Results.—Sequelae of bacterial meningitis caused by *H influenzae* b were equal to or exceeded rates of sequelae described in other children in the United States. After *H influenzae* b meningitis, motor abnormalities (29%) and hydrocephalus (7%) occurred two to four times more often in Alaska Native children than in children in other parts of the United States. Differences in severity of *H influenzae* b sequelae could not be accounted for by microbiologic markers of the *H influenzae* b strain, including ampicillin sensitivity, biotype, outer membrane protein type, or electropherotype. Numbers of cases of *S pneumoniae* meningitis were too small for statistically valid comparison, but sequelae of *S pneumoniae* meningitis occurred in roughly equal proportion as sequelae of *H influenzae* b meningitis. The HTPS was applied to Alaska Native children with *H influenzae* b meningitis and was found to be very accurate in predicting children with major sequelae. Analysis of the prognostic factors used in deriving the HTPS revealed a unique set of predictors for sequelae in Alaska Native children: seizures at admission, glucose levels in cerebrospinal fluid of less than 1.1 mmol/L; and male gender, with a significant predictive interaction between male gender and age less than 6 months at admission.

Conclusions.—Alaska Native children suffer greater neurologic morbidity as a result of *H influenzae* b meningitis than do their non-Native counterparts. The HTPS was a good predictor of major sequelae in Alaska Native children with *H influenzae* b or *S pneumoniae* meningitis and could be useful in determining which patients need referral to a tertiary care center.

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Reduction of the incidence of bacterial meningitis in infants is a national and international priority that is being addressed by efforts to develop effective vaccines against the primary agents: *Haemophilus influenzae* type b, *Streptococcus pneumoniae,* and *Neisseria meningitidis.*[1] The incidence of *H influenzae* b and *S pneumoniae* is five to 10 times higher in Alaska Natives than in the general population of the United States and non-Native Alaskans and two to three times that of Native Americans from the lower 48 states and Canada.[2-9]

Mortality due to bacterial meningitis has been reported for many populations and has decreased markedly in the antibiotic era.[1-11] The case-fatality rate of bacterial meningitis in Alaska Natives (*H influenzae* b, 3.8%,[2] and *S pneumoniae,* 14%[3]) is comparable to that of the general population of the United States (*H influenzae* b, 5.0%,[1] and *S pneumoniae,* 26%[3]), but the question of meningitis morbidity and long-term sequelae in survivors has not yet been addressed in Alaska Natives.

One study[12] of all cases of bacterial meningitides in the Canadian Northwest Territories in which all patients were

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followed up to monitor development of sequelae found a high rate of serious sequelae in Native Canadians who survived the meningitides (14 [44%] of 32 patients). However, results of another study[6] in Arizona in which 62% of patients were followed up to monitor development of sequelae suggested lower rates of serious sequelae after all types of bacterial meningitis in Native American children (27 [30%] of 89 surviving children had serious sequelae). Neither of these studies separated the sequelae according to causative organism or described methods of assessing sequelae.

Herson and Todd[13] described a prognostic scoring system for *H influenzae* b meningitis that predicts serious morbidity based on clinical parameters of the infection present at diagnosis. Among other factors, this scoring system suggests that age less than 1 year at development of *H influenzae* b meningitis is a significant predictor of morbidity. Alaska Natives are much more likely to develop *H influenzae* b meningitis in the first 6 months of life than are children in the general population of the United States (34% to 48%[2,14] vs 19%[7]). This could make the risk of serious sequelae in Alaska Native children considerably higher in light of the reported increase in subdural effusions and short-term morbidity in infants younger than age 6 months with *H influenzae* b or *S pneumoniae* meningitis.[15] The Herson-Todd scoring system might be useful for selecting patients for transfer to an intensive care unit or for determining if steroids should be administered in a high-risk population such as Alaska Natives. However, the system was developed in an urban population with a much different incidence and epidemiologic picture of disease.

We assessed *H influenzae* b and *S pneumoniae* sequelae and evaluated the Herson-Todd scoring system in Alaska Natives in the Yukon Kuskokwim Delta (YKD), an area of Alaska with one of the highest rates of both types of infection.[2,3] The YKD service unit is a 150 400-square kilometer area of southwestern Alaska with a population of Yupik Eskimos (82%), Athapaskan Indians (5%), and non-Natives (13%). The 1980 census estimate for total population in the region was 16 105, and 1989 estimates by the Indian Health Service and the state of Alaska indicate a population of approximately 20 000.[16] Approximately 17% of the YKD population live in the town of Bethel, which has the only hospital (43 beds), laboratory, and physician-staffed clinic in the region. The rest of the population lives in 52 separate villages. A unified and centralized health care system, hospital laboratory, and patient record system and a uniform approach to diagnosis and treatment of meningitis sequelae made possible detailed surveillance and follow-up of patients with meningitis.

By reviewing records of cases identified by ongoing surveillance between 1980 and 1989, we were able to (1) determine the frequency and severity of *H influenzae* b and *S pneumoniae* meningitis sequelae in Alaska Native children, (2) compare morbidity and mortality of *H influenzae* b meningitis with *S pneumoniae* meningitis, and (3) evaluate the applicability of the Herson-Todd scoring system to both *H influenzae* b and *S pneumoniae* meningitis in this high-risk population.

PATIENTS AND METHODS

All cases of *H influenzae* b or *S pneumoniae* meningitis in residents of the YKD service unit were identified from surveillance records originating between January 1, 1980, and December 31, 1988. The subjects of this study were Alaska Native patients younger than age 5 years. The surveillance systems have been previously described in detail.[2,3] In brief, all cases of *H influenzae* b and *S pneumoniae* meningitis identified by culture of sterile body fluids at the YKD regional Indian Health Service hospital in Bethel, Alaska, were included, as were cases of *H influenzae* b or *S pneumoniae* meningitis in YKD residents cared for at referral hospitals and identified by statewide *H influenzae* b and *S pneumoniae* surveillance. Meningitis was defined as cerebrospinal fluid (CSF) pleocytosis documented with laboratory findings and culture of *H influenzae* b or *S pneumoniae* from CSF or CSF pleocytosis, the presence of *H influenzae* b antigen in CSF identified with latex particle agglutination, and a positive blood culture for *H influenzae* b or *S pneumoniae*. *Haemophilus influenzae* b and *S pneumoniae* isolates were sent to the Arctic Investigations Program, Centers for Disease Control, Anchorage, Alaska, for confirmation of organism, serotype (for *S pneumoniae*), biotype (for *H influenzae* b), and antibiotic sensitivity.

Haemophilus influenzae b isolates were further characterized at the Harbor-UCLA Medical Center, Torrance, Calif, in the following ways: (1) Serotyping was performed with slide agglutination and counter-immunoelectrophoresis using typing sera available from the Centers for Disease Control, and selected strains were probed with the cap gene using Southern blot analysis.[17] (2) Outer membrane proteins were extracted from the cell wall with Triton X-100[18] and typed using sodium dodecyl sulfate–polyacrylamide gel electrophoresis with a 10% Laemmli gel and 3-20% Lugtenberg gradient gel. The outer membrane protein classification scheme used was as developed at Washington University.[19,20] (3) Techniques of horizontal starch-gel electrophoresis and the demonstration of specific enzyme activity have been described.[21,22] Electromorphs (allozymes) of each of the 17 enzymes were electropherotypes (ETs).[20,22]

All YKD and referral hospital charts of identified patients were reviewed using a standardized data abstraction form that included clinical and laboratory data at the onset of illness as well as all available follow-up clinical, laboratory, and developmental data obtained during subsequent years. The YKD service unit had a developmental assessment program for evaluation of patients with meningitis during the entire study period. This program required that all children younger than age 3 years with a history of meningitis be evaluated by the Infant Learning Program at least once. This program consisted of administration of several developmental screening tests by trained personnel, including the Denver Developmental Screening Test, the Learning Assessment Profile, and the Sewall Early Education Development Profile. The initial evaluation was scheduled for 4 to 6 weeks after discharge from the hospital and consisted of a behavioral audiologic examination and examination of neurodevelopmental and general physical condition. Brain-stem evoked-response audiometry was performed only rarely in infants sent to the tertiary referral center in Anchorage. If this initial follow-up appointment was not kept, Infant Learning Program personnel performed the three developmental screening tests described in the patient's home village as soon as possible within the next 2 months. If no abnormalities were found with these assessments, the patients were not followed up further by the program unless an abnormality was identified by physicians in subsequent follow-up. If abnormalities were found with Infant Learning Program, physician, or audiologic screening, the patient was referred to an evaluation team consisting of a pediatrician, occupational therapist, physical therapist, audiologist, speech pathologist, and developmental psychologist. All patient evaluations were performed by the same people during the 9-year study period. Occupational and physical therapy evaluations were performed by two or three therapists in each profession, while audiology, speech pathology, and developmental psychology evaluations were performed by one individual in each profession. The developmental psychologist used the Bayley Scales of Mental Functioning, Gesell developmental schedule, Catell Infant Intelligence Scale, Stanford-Binet Scale, or

Wechsler Intelligence Scale for Children-revised for formal evaluation, depending on the age of the patient at evaluation. Follow-up was continued until the team deemed it no longer necessary based on results of the assessments listed above. All the information from these evaluations was available for review either in the patients' charts or in the files of the Infant Learning Program. This study was based on the presence or absence of abnormalities noted by members of the developmental team and not on quantitative values of any of the evaluations.

For comparison of our data with the data of Herson and Todd,[13] major sequelae were defined as any of the following conditions: blindness, hydrocephalus, institutionalization, severe mental retardation, quadriplegia, microcephaly, uncontrolled seizures, and death. Minor sequelae included transient or permanent hearing loss, hemiparesis, motor delay, language delay, subdural effusion, and mild mental retardation. Some sequelae classified as minor by Herson and Todd[13] may be considered major sequelae by other investigators, but the classification system of Herson and Todd was used in this comparative study.

Blindness was determined with results of an ophthalmologic examination, and hydrocephalus, subdural effusion, cortical atrophy, and the extent of such lesions were determined based on a radiologist's interpretation of a computed tomographic scan and/or cranial ultrasound study. For our analysis, cortical atrophy (present in three patients with *H influenzae* b and two patients with *S pneumoniae*) was classified as hydrocephalus due to the presence of ventriculomegaly. Degree of mental retardation was determined by the psychologist and not by our interpretation of test scores. Seizures were defined as sequelae if they developed after diagnosis of meningitis and persisted for more than 10 days after start of treatment. Seizures occurring only at admission or during therapy were not considered sequelae, although seizures occurring at admission were analyzed as predictors of later sequelae.

Gross or fine motor delay (eg, hemiplegia) and language delay were defined as levels of performance less than expected for age at any examination of these parameters by a pediatrician, psychologist, speech pathologist (for evaluation of language delay only), or occupational or physical therapist. Only a hearing loss of greater than 30 dB that was determined by an audiologist to be a probable sensorineural loss was accepted as a hearing loss for this study.

Patients with preexisting conditions, such as seizures and congenital anomalies, that might be associated with later developmental deficits, or patients with developmental delay before acquiring meningitis, were excluded from analyses.

To compare rates of *H influenzae* b meningitis–related morbidity in Alaska Natives with data from the general population of the United States, we used results of the study by Ferry et al.[10] This study was chosen for comparison because of the similarity in broad range of sequelae assessed in that study, lengths of patient follow-up, therapy, definitions of sequelae, and sample size. For comparison with the study of Tennessee infants by Ferry et al,[10] we adjusted our definitions to match those used in the Tennessee study. Consequently, we compared isolated language delay (unassociated with hearing loss) and combined motor delay with hemiparesis.

STATISTICAL ANALYSES

Percentages of patients developing sequelae were compared using the χ^2 test and Fisher's Exact Test as appropriate. Analyses of the degree of severity of sequelae were performed using a test for the linear trend in proportions. To assess possible confounding factors and interactions among the predictors of sequelae, multiple logistic regression was used. All *P* values are two-sided, except those for Fisher's Exact Test, which are one-sided.

RESULTS

During the 9 years of the study, 51 cases of *H influenzae* b meningitis and 13 cases of *S pneumoniae* meningitis (a total of 64 cases) were identified in 63 patients in the YKD. One patient developed both forms of meningitis and for study purposes was considered to represent two cases of meningitis. All cases except three occurred in Yupik Eskimos. Three cases of *H influenzae* b meningitis were identified in Athapaskan Indians. Age at diagnosis ranged from 3½ weeks to 30 months, with 28 patients (44%) being younger than age 6 months and 48 (75%) being younger than age 1 year at diagnosis. Mean and median age at diagnosis was 8 months. Thirty-three (52%) of the cases occurred in boys. Three (5.9%) of 51 patients with *H influenzae* b died as a result of meningitis, and one patient with *S pneumoniae* died during a long hospitalization that began with *S pneumoniae* meningitis but resulted in death caused by other infections.

Ten patients were excluded from further analyses because of potential confounding neurologic or other preexisting conditions that might have caused or contributed to later developmental deficits. These 10 patients included one patient who first suffered *S pneumonaie* and later developed *H influenzae* b meningitis, leaving 53 cases for analysis. All analyses of clinical correlates of sequelae were repeated to include this group of excluded patients, and the results did not change.

Of the 51 surviving study patients, mean and median follow-up periods were 35 months, with 34 patients (67%) being followed up for more than 2 years and 12 (24%) being followed up for less than 1 year. Mean length of follow-up and proportion with follow-up of more than 2 years did not differ between patients without sequelae and patients with sequelae. (Patients without sequelae were followed up for a mean of 38.7 months, and 70% of these patients were followed up for more than 2 years. Patients with sequelae were followed up for a mean of 34.5 months, and 62% of these patients were followed up for more than 2 years.) Median and range of follow-up for patients with major, minor, or no sequelae were as follows: major sequelae, median, 9 months (range, 6 to 82 months); minor sequelae, median, 41 months (range, 12 to 82 months); no sequelae, median, 35 months (range, 2 to 99 months). Of the 10 patients with major sequelae, one died within 8 months of diagnosis and four were diagnosed in the last 7 months of 1987. For these four, follow-up time was limited by the December 1988 deadline for chart reviews. The median times after discharge from the hospital to first audiologic screening were 2 and 5 weeks for patients with *S pneumoniae* and *H influenzae* b meningitis, respectively. One (10%) of 10 patients with *S pneumoniae* and four (9.3%) of 43 patients with *H influenzae* b meningitis did not undergo audiologic screening but were examined and followed up by physicians. Most patients underwent several audiologic examinations.

Sequelae of the 53 study patients (including two who died as a result of meningitis) without confounding premeningitis histories are shown in Table 1. The denominator used for *H influenzae* b cases in this table includes death as a sequela, whereas rates of sequelae of *H influenzae* b meningitis that exclude death are shown in Table 2. Among these 53 study patients, two with *H influenzae* b meningitis and none with *S pneumoniae* meningitis died as a result of meningitis, giving a case-fatality rate of 4.6% for *H influenzae* b, none for *S pneumoniae*, and 3.8% overall. Overall, 10 (19%) of the 53 patients described in Table 1 experienced at least one major sequela, and 13 patients (25%) experienced at least one minor sequela. The most

Table 1.—Sequelae by Disease Organism*

Sequelae	*Haemophilus influenzae* Type b (n=43)	*Streptococcus pneumoniae* (n=10)	Total (N=53)
Major†	8 (19)	2 (20)	**10** (19)
Blindness	0	0	**0**
Hydrocephalus	3 (7)	2 (20)	**5** (9)
Severe mental retardation	1 (2)	1 (10)	**2** (4)
Quadriplegia	0	0	**0**
Seizures	4 (9)	1 (10)	**5** (9)
Death	2 (5)	0	**2** (4)
Minor‡	11 (26)	2 (20)	**13** (25)
Hearing loss	5 (12)	1 (10)	**6** (11)
Hemiparesis	6 (14)	2 (20)	**8** (15)
Motor delay	6 (14)	1 (10)	**7** (13)
Central nervous system palsy	0	0	**0**
Subdural effusion	2 (5)	0	**2** (4)
Mild mental retardation	3 (7)	0	**3** (6)
Language delay	14 (33)	2 (20)	**16** (30)

*Values are number (percentage) of cases in each category, except for rows one and eight, which are number (percentage) of patients. Some patients had more than one sequela.

†Data in this row represent infants with major sequelae only. Some infants had major and minor sequelae.

‡Data in this row represent infants with minor sequelae only. Some infants had minor and major sequelae.

Table 2.—Comparison of Sequelae of *Haemophilus influenzae* Type b Meningitis in Alaska Native vs Tennessee Infants*

	Tennessee Infants (N=53)†	Alaska Native Infants (N=43)
No. of deaths	3 (6)	2 (5)
No. of patients alive at follow-up	46 (87)	41 (95)
Results of follow-up		
Normal	23 (50)	24 (59)
Hearing loss	9 (20)	5 (12)
Mental retardation	5 (11)	4 (10)
Hydrocephalus	1 (2)	3 (7)
Seizures	2 (4)	4 (10)
Motor abnormality†	3 (7)	12 (29)
Language delay‡	7 (15)	6 (15)

*Values are number (percentage) of cases, except for the first two rows, which are number (percentage) of patients. Some patients had more than one abnormal result.

†Four infants were unavailable for follow-up.

‡Includes hemiparesis.

§Includes only isolated language delay.

common sequela experienced by the latter group was language delay (30%). When language delay was assessed as an isolated deficit in the absence of hearing loss or mental retardation, six cases (15%) were identified (Table 2). The proportion of patients with major sequelae did not differ significantly based on disease organism ($P=.61$ by Fisher's Exact Test), nor did the proportion of patients developing any type of sequelae differ significantly based on disease organism ($P=.55$ by Fisher's Exact Test).

Results of a comparison of *H influenzae* b meningitis–related sequelae in Alaska Natives and in a non-Native population in Tennessee are shown in Table 2. Eighty percent of the infants in the Tennessee study were Caucasian, and the remaining 20% were African-American.[10] These data show a higher incidence of hydrocephalus, seizures, and motor abnormalities and a lower incidence of hearing deficits in Alaska Native children.

Table 3.—Association of Risk Factors With Sequelae

Factors	Sequelae: Major	Minor	None	*P**
On admission				
Coma†	1/10	0/13	0/30	.189
Systolic blood pressure <60 mm Hg†	2/8	0/6	0/15	.069
Temperature <36.6°C†	0/10	1/13	0/30	.811
Seizures†	9/10	5/13	3/30	<.001
Symptoms >3 d†	1/10	4/13	3/30	.617
Age at diagnosis				
<12 mo†	9/10	9/13	23/30	.273
<6 mo	8/10	6/13	12/30	.033
Mean corpuscular volume ≥80 fL	6/9	2/10	5/26	.011
Hemoglobin <110 g/L†	8/9	8/12	23/28	.403
White blood cell count				
<5.0×10^9/L	3/9	0/13	1/30	.014
<10.0×10^9/L	5/9	4/13	7/30	.076
Protein				
>1.00 g/L‡	10/10	8/12	20/27	.058
<2.00 g/L‡	6/10	4/12	6/27	.048
White blood cell count <1000×10^6/L†‡	3/10	4/13	6/30	.969
Glucose <1.1 mmol/L†‡	9/10	8/13	12/30	.013
Other				
Male gender	8/10	8/13	11/30	.044
Maternal age ≥30 y	3/10	3/12	2/30	.171
Gestational age <36 wk	3/10	3/12	0/30	.018
Birth weight <2500 g	2/10	1/13	1/30	.157
Apgar score <9	0/10	2/12	4/30	.258

*Major sequelae vs minor sequelae and no sequela combined. Except for *P* values, values are number of cases/number of patients for whom the specified information was available.

†Regression parameters in the Herson-Todd model.

‡In cerebrospinal fluid.

Clinical Correlation

The data were examined for associations between severity of disease outcome and a variety of demographic, neonatal, and clinical factors at admission (Table 3). Factors analyzed included those found to be significant predictors of *H influenzae* b meningitis–related sequelae in the Herson-Todd study[13] and others that we thought might be relevant. Comparisons of all patients with major and minor sequelae vs patients with no detectable sequelae on follow-up, comparisons of patients with major vs minor or no sequelae, and comparisons of all three groups (major, minor, or no sequelae) by linear trend test were performed and showed similar results. Presence of seizures on admission was the independent factor most strongly associated with major sequelae.

The Herson-Todd scoring system was applied to the patients, and sufficient information to classify a patient's total score as less than 4.5 or 4.5 or higher (the values determined in the previous study[13] to distinguish patients likely to have severe sequelae from those likely to have minor or no sequelae, respectively) was available for 48 of the 53 cases analyzed. Of the 40 patients with scores of less than 4.5, only two experienced major sequelae, whereas of eight patients with scores of 4.5 or higher, seven had major sequelae. Thus, the development of minor or major sequelae was incorrectly predicted in three patients (6.3%), which is not significantly different than the rate reported by Herson and Todd.[13] When this classification system is evaluated by organism, two of 39 cases of *H influenzae* b (5.1%) and one of nine cases of *S pneumoniae* (11.1%) were misclassified ($P = .472$ by Fisher's Exact Test).

Multiple logistic regression analysis was performed comparing patients with major sequelae with all other patients. All independent factors listed in Table 3 were examined as well as interactions of the factors in Table 3 with age less than 6 months and gender. Using a forward selection approach with presence or absence of major sequelae in our patients as a dependent variable, we arrived at a model that included (in the order of inclusion) presence of seizures, glucose levels of less than 1.1 mmol/L in CSF, and male gender (relative risk, 62.8, 28.5, and 10.2, respectively; $P < .05$). There was a significant interaction between age and gender. However, age less than 6 months and the interaction of age and gender are not included in the regression model because they did not achieve the 5% significance level in the model. Although equal numbers of boys and girls had disease during the first 6 months of life ($n = 13$ for each), significantly more boys than girls had major sequelae (boys, seven; girls, one; $P = .015$ by Fisher's Exact Test). No such difference was seen in the patients diagnosed after age 6 months (one of 14 boys and one of 13 girls experienced major sequelae; $P = .74$ by Fisher's Exact Test).

Treatment

All *H influenzae* b– and *S pneumoniae*–infected patients received a minimum of 10 days of parenteral antibiotics for meningitis therapy. Forty-seven of 51 *H influenzae* b–infected patients received only ampicillin sodium and chloramphenicol sodium succinate. Three of the remaining four patients received ceftriaxone sodium for most of their treatment course, and one of these three patients was among those infants excluded. One *H influenzae* b-infected patient received cefuroxime sodium only for the first day of therapy, followed by ampicillin and chloramphenicol. All patients with *S pneumoniae* meningitis received ampicillin sodium or penicillin and chloramphenicol for their primary treatment course. One of these patients received cefotaxime sodium for the first day and finished the treatment course with penicillin.

Microbiology

Cultures were available for biotyping and antibiotic-resistance testing for 41 of the 43 *H influenzae* b–infected patients (eight of the original 51 patients with *H influenzae* b were excluded because of preexisting conditions). All invasive isolates were confirmed to be type b. Neither *H influenzae* b biotype nor ampicillin resistance in *H influenzae* b isolates varied significantly by category of outcome. Outer membrane protein typing of *H influenzae* b was performed for 38 of the 43 isolates, and electropherotypes were available for 20 isolates. The most common outer membrane protein types were 2L (28%), 3L (26%), 5L (18%), and 13L (18%). The predominant ETs were 12.7 (35%) and 18 (35%). When stratifying the outcome categories by outer membrane protein and ET, no association with protective or virulence strain markers could be identified.

Six of 10 isolates from patients infected with *S pneumoniae* were available for serotyping at the Centers for Disease Control. Each of the *S pneumoniae* isolates had a different serotype (1, 4, 7F, 12F, 13C, 33F), and all were susceptible to penicillin, ampicillin, and chloramphenicol. The numbers of isolates were too small for meaningful analysis of relationships to sequelae of *S pneumoniae*–infected patients.

COMMENT

Because we found no significant differences in sequelae between the *S pneumoniae*– and *H influenzae* b–infected patients, many of the conclusions about *H influenzae* b meningitis may also apply to sequelae of *S pneumoniae*. A higher rate of sequelae has been observed[11] for children with *S pneumoniae* meningitis. However, because of small numbers of *S pneumoniae*–infected patients, there was a relative lack of power to detect significant differences in incidence of sequelae in patients with *H influenzae* b meningitis vs patients with *S pneumoniae* meningitis, and firm conclusions cannot be drawn. Therefore, unless otherwise specified, this discussion of sequelae is concerned with outcome data of patients with *H influenzae* b.

A primary objective was to determine if *H influenzae* b meningitis–related sequelae might be more severe in Alaska Native infants than in infants in the general population of the United States. Such increased severity is suspected because Alaska Native children typically develop *H influenzae* b meningitis at a younger age than do other children in the United States and Canada,[2,7,9,14] with a peak incidence in Yupik Eskimos at age 4 to 5 months.[14] Age less than 6 months at diagnosis of *H influenzae* b meningitis has been associated with higher morbidity.[15] To address this question, we compared frequency of *H influenzae* b meningitis sequelae in Alaska Native children with data from a 6-year prospective longitudinal study (from 1975 to 1981) of children with *H influenzae* b meningitis in Tennessee.[10] We recognize the hazards of applying statistical tests to data from different studies, but have attempted such a comparison for the sake of discussion. We found that only incidence of motor abnormalities, which Alaska Natives were four times more likely to experience, differed significantly ($P = .005$). This may reflect the small numbers in certain categories in both studies, and it could also reflect the differing methods used. All studies of meningitis sequelae reported thus far are limited by relatively small numbers of patients available for analysis.

Pomeroy et al[23] reported seizure disorders occurring within 2 to 8 years of discharge from the hospital in nine (7.6%) of 118 nonfebrile patients with *H influenzae* b meningitis and in three (10.0%) of 30 nonfebrile patients with *S pneumoniae* meningitis. This is comparable to our finding of four (9.3%) of 43 nonfebrile patients with *H influenzae* b meningitis and five (9.4%) of 53 nonfebrile patients with either *H influenzae* b or *S pneumoniae* meningitis experiencing onset of seizures within 2 to 6 years of discharge from the hospital.

Sensorineural hearing loss appeared to occur somewhat more often in children from Tennessee than in Alaska Natives (20% vs 12%), but less often in children from St Louis, Mo, (6%)[24] than in Alaska Natives. This could be due to difficulty in distinguishing conductive losses from sensorineural losses with standard audiologic techniques for children younger than age 5 years. The high incidence of otitis media in Alaska Native children[25,26] makes assessment of sensorineural hearing loss more difficult in long-term follow-up, and we used restrictive criteria for assigning sensorineural hearing loss. If there was any question about the origin of the hearing loss, the finding was assigned to the category, "unknown cause," resulting in potential underdiagnosis of sensorineural hearing loss in this population.

Our data likely reflect an underestimate of morbidity, considering the strict exclusion criteria used for analysis of patients with preexisting conditions that might affect later development of the sequelae examined. Of the 10 excluded patients, five developed severe sequelae. In at least three of the five excluded patients, the preexisting conditions (aseptic meningitis, neonatal apnea/possible seizure, and language delay) would not seem likely to be related to the plethora of meningitis-related morbidity in the patients (severe mental retardation and language delay in all three and blindness, poorly controlled seizures, and motor abnormalities in the other two). Therefore, we think it likely that, in several categories, Alaska Native children are more likely to develop sequelae of *H influenzae* b and *S pneumoniae* meningitis than are children in the general population of the United States.

The prevailing standard of care and antibiotic therapy was similar for the Tennessee[10] and Alaskan studies. Most of our patients (94%) received ampicillin and chloramphenicol. The only other regimen used for long-term therapy was ceftriaxone, which was used by three patients, one of whom was excluded from analysis. It has been shown that there is no apparent difference in sequelae and outcome in children with *H influenzae* b or *S pneumoniae* meningitis treated with ceftriaxone[27-29] or cefotaxime[29,30] compared with children treated with ampicillin and chloramphenicol. Therefore, therapeutic regimen did not account for the increased incidence of sequelae in Alaska Native children in this study.

This is the first study attempting to correlate the severity of *H influenzae* b meningitis with microbiologic markers, including biotype, ampicillin resistance, type of outer membrane protein, and ET. The sample size of type isolates and the number of patients with severe outcomes were somewhat limited in our study, but there was not even a trend toward either better or more severe outcome with any specific strain. Clearly, type b capsule is the major determinant of virulence, but the other typing markers did not appear to be linked to virulence genes of the organisms. Thus, any difference in microbiologic markers of disease causing *H influenzae* b strains in the Alaska Native population would not be likely to account for the greater incidence and severity of sequelae of *H influenzae* b meningitis seen in this population.

The Herson-Todd model was a relatively good predictor of major sequelae in Alaska Natives. By making a calculation based on data from the original study,[13] the misclassification rate for Herson and Todd was 2.7% (two of 73 patients) compared with 5.1% for patients with *H influenzae* b, 11.1% for patients with *S pneumoniae*, and 6.3% for patients with *H influenzae* b and *S pneumoniae* in our study. We cannot state with certainty how useful the model may be for pneumococcal meningitis, as our sample size for *S pneumoniae* meningitis was small. However, if results of our study of *S pneumoniae* meningitis can be verified in a larger series of patients, our data suggest that the model may be useful.

The Herson-Todd scoring system could also be useful in deciding which meningitic children should be referred to tertiary care centers in extremely isolated settings such as rural Alaska. The additional predictive factors (interaction of gender and age) identified in our patients may also be useful in identifying which patients should receive tertiary care.

Results of this study strongly suggest that Alaska Native children suffer slightly greater *H influenzae* b meningitis–related morbidity than do their non-Native counterparts. We suspect that this may be true for other Native American populations in which *H influenzae* b meningitis occurs at younger ages than in the general population.[4,5,9,12] These data provide a selection basis for referral of Alaska Native patients with *H influenzae* b meningitis to tertiary care centers. The continuing occurrence of meningitis and subsequent morbidity despite treatment with antibiotics and anti-inflammatory agents[31] makes the continued focus on delivery of efficacious vaccines of the utmost importance. This approach offers the best hope for prevention of the diseases in question and may ultimately make questions of mortality and morbidity less pressing.

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ARCHIVES OF SURGERY

Delayed Primary Wound Closure Using Skin Tapes for Advanced Appendicitis in Children: A Prospective, Controlled Study

Tat M. Tsang, MBBS, FRCSE; Paul K. H. Tam, MBBS, ChM, FRCSE; Htut Saing, MBBS, FRCSE (*Arch Surg.* 1992;127:451-453)

Long-term Outcome of Neonatal Meningitis

Sofia M. Franco, MD; Victoria E. Cornelius, MD; Billy F. Andrews, MD

• *Objective.*—To determine the long-term outcome of neonatal bacterial meningitis and the relationship between the outcome and specific features in the acute stage of the disease; and to compare the outcome between infants with neonatal meningitis and high-risk infants without meningitis.

***Design.*—Prospective clinical evaluations of 21 survivors of meningitis and 21 matched controls who were retrospectively selected from a high-risk patient population.**

***Setting.*—Program of follow-up performed at the Children and Youth Project's High Risk Center of the Department of Pediatrics, University of Louisville, Louisville, Ky. Neonates were inborn at a university hospital with a high-risk obstetric unit and level III nursery.**

***Patients.*—Twenty-six consecutive neonates born between 1970 and 1980 with culture-proven bacterial meningitis, excluding neonates with congenital neurologic defects. Nineteen of 21 survivors and 21 controls matched by age, sex, race, birth weight, and gestational age were followed up from 1 to 14 years (mean, 7.8 years). Both survivors and controls fell below the federal poverty guidelines.**

***Results.*—Gram-positive meningitis was twice as common as gram-negative meningitis with co-occurrence of meningitis and sepsis in half of the cases. Neonates with gram-positive meningitis and higher birth weight had a higher survival rate, but this finding was not statistically significant. The mortality rate in neonates with gram-negative meningitis was almost three times higher than that of neonates with gram-positive meningitis, but no significant difference was observed between their morbidity rates. Eight (38%) of 21 survivors were normal, while another eight (38%) and five (24%) had mild and moderate to severe sequelae, respectively. Survivors of meningitis had lower IQ scores and more severe sequelae than matched controls.**

***Conclusion.*—Neonatal bacterial meningitis results in poorer long-term outcome than in controls, but improved outcome compared with previous studies of neonatal meningitis.**

(*AJDC.* 1992;146:567-571)

The mortality and morbidity rates for neonatal bacterial meningitis remain high, despite the newer bactericidal antibiotics and the evolution of specialized supportive care in neonatal intensive care units. A mortality rate of 15% to 60% is reported worldwide with significant neurologic and developmental abnormalities observed in 30% to 50% of survivors.[1-6] In a 14-year review of this problem in neonates born between 1973 and 1986, Bell and colleagues[7] observed that the rates of mortality and survival without handicaps were largely unchanged from earlier years. Previous studies[2,4,8,9] reported clinical and laboratory features predictive of immediate and long-term outcome of neonatal meningitis.

A study was undertaken in our institution to determine both the long-term outcome of bacterial meningitis diagnosed in the first month of life and the relationship between the outcome and specific features in the acute stage of the disease.

PATIENTS, MATERIALS, AND METHODS

All infants born at the Louisville (Ky) General Hospital between 1970 and 1980 in whom a positive bacterial culture was obtained from the cerebrospinal fluid (CSF) in the first month of life were admitted to the study. Infants with congenital neurologic defects were excluded from the study. All infants were born in this center, which included a high-risk obstetrics unit and level III nursery. These infants are part of a larger patient population born in the same hospital who were enrolled in a longitudinal study at the Children and Youth Project's Comprehensive Health Care Center because of prematurity and other medical or social high-risk conditions. To be able to compare the outcome of infants with meningitis with the outcome of other high-risk infants without meningitis, matched controls were retrospectively selected from the project's high-risk patient population. Twenty-one survivors of meningitis were matched by age, sex, race, birth weight, and gestational age. Both controls and survivors of meningitis received the same prospective follow-up evaluations and both groups had family income below the federal poverty guidelines.

On entry into the project, perinatal variables were recorded, including birth weight, gestational age, Apgar scores, and resuscitation measures. Following an explanation of the project's follow-up, informed consent was obtained from a parent of each enrollee. The follow-up program, which began shortly after birth through age 12 years, included physical, neurologic, and developmental assessments at ages 2, 4, 6, 9, 12, 18, and 24 months, and yearly thereafter. Speech and language evaluation at ages 1, 2, and 3 years and annual vision and hearing screens were provided along with routine preventive and episodic illness care. In addition, psychometric testing was performed at ages 3 and 6 years using the Stanford-Binet Intelligence Scale (form L-M) and, where appropriate, the Cattell Infant Intelligence Scale, Wechsler Intelligence Scale for Children, Wechsler Intelligence Scale for Children–Revised, and Wechsler Preschool and Primary Scales of Intelligence were also administered. Some children underwent psychometric testing earlier or later than the previously specified age. Information on scholastic performance was obtained from schools attended by school-aged survivors.

Student's *t* tests and χ^2 analysis were used for statistical analysis.

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Table 1.—Number of Cases and Survival After Diagnosis of Neonatal Meningitis, by Organism, 1970-1980

	No. of Cases (N=26)	No. of Patients With Positive Cultures		No. (%) of Survivors
		Cerebrospinal Fluid and Blood	Cerebrospinal Fluid	
Group B *Streptococcus*	11	8	3	10 (91)
Streptococcus viridans	3	. . .	3	3 (100)
Group D *Streptococcus*	1	. . .	1	1 (100)
Staphylococcus aureus	1	. . .	1	1 (100)
Staphylococcus epidermidis	1	1	. . .	0
Escherichia coli	7	2	5	5 (71)
Klebsiella aerobacter	2	2	. . .	1 (50)

Table 2.—Cerebrospinal Fluid (CSF) Findings in Relation to Survival

CSF Findings	No. of Survivors	No. of Deaths	*P*	χ^2
Protein				
≤5 g/L	14	2	<.5	405
>5 g/L	7	2		
Glucose				
≤1.7 mmol/L	8	2	<.4	.649
>1.7 mmol/L	12	2		
White blood cell count				
≤1x10⁹/L	13	2	≤.4	.79
>1x10⁹/L	8	3		

RESULTS

Twenty-six neonates among 27 075 live births at Louisville General Hospital from 1970 to 1980 had culture-proven bacterial meningitis, an incidence of 0.96 per 1000 live births. Five infants (19%) died in the neonatal period and 21 (81%) survived; 19 patients were available for long-term follow-up, whereas the remaining two survivors were not available for long-term follow-up although they were physically and developmentally normal at 5 weeks following hospital discharge.

An almost equal race distribution was observed (14 black and 12 white neonates). There were 17 girls and nine boys, a 2:1 sex ratio. While 22 neonates were of appropriate size for gestational age, four were small for gestational age, all of whom survived. Thirteen neonates had birth weights less than 2500 g and 13 weighed 2500 g or greater. There were nine neonates younger than 36 weeks gestational age and 17 neonates 36 weeks or older. No significant difference was noted in the method of delivery, resuscitation measures, or Apgar scores between the study and control groups.

Sixty-two percent (16 of 26) of the neonates had onset of symptoms in the first week of life, including three who died, while 38% (10 of 26) had initial symptoms beyond the first week of life. Statistical correlation of survival to onset of symptoms could not be made because of the small number who died. The majority of the symptoms were nonspecific and included respiratory distress, fever, jaundice, lethargy, poor feeding, irritability, apnea, bradycardia, and high-pitched or weak cry. Manifestations observed late in the course of the illness included seizures in seven neonates, and opisthotonos and cranial nerve palsy each noted in one neonate.

Gram-positive organisms accounted for 65% of the isolates with group B *Streptococcus* as the most common pathogen often isolated from both CSF and blood (Table 1). The differences in CSF, glucose, protein, and white blood cell count levels between patients who died and those who survived were not statistically significant (Table 2).

Computed tomography of the head performed in seven patients in the neonatal period revealed hydrocephalus in four patients, hydrocephalus and intraventricular hemorrhage in one, and parenchymal and subarachnoid hemorrhages in two. Other early neurologic sequelae noted were seizures in two neonates and paresis and cranial nerve palsy each in one neonate.

LONG-TERM OUTCOME

Nineteen survivors were followed up from 1 to 14 years (mean, 7.8 years; median, 4.5 years); the control group was followed up for a comparable period. Table 3 shows details regarding the outcome of neonatal meningitis by weight and gestational age. As apparent in this table, higher birth weight (≥2500 g) and older gestational age (≥36 weeks) forebode lower mortality, but this did not prove to be statistically significant, probably as a result of small numbers. Abnormal sequelae in the survivors were comparable. Table 4 shows the outcome in the control group by birth weight and gestational age. The numbers of patients with normal and abnormal outcome were similar between groups; however, the sequelae noted in the study group tended to be moderate in degree, while those in the control group were milder.

Table 5 shows IQ scores of survivors of meningitis and controls. Seventy-three percent (11 of 15) of survivors of meningitis had borderline to average intelligence, while 27% (4 of 15) had either mild or moderate mental retardation. In contrast, all 14 control patients had borderline to average intelligence; this difference between the control and meningitis groups was statistically significant ($P<.02$). The two patients in the meningitis group with moderate mental retardation had either group B *Streptococcus* or *Streptococcus viridans* as the causative organism, while the two patients with mild mental retardation were survivors of *Escherichia coli* or *Klebsiella* meningitis. No significant difference was noted in vision, hearing, and language evaluations between the study and control groups (Table 6). Two survivors of meningitis had moderate myopia and one had optic atrophy, whereas milder myopia and astigmatism were noted in the control group. A survivor of group B *Streptococcus* meningitis was the only patient with sensorineural hearing loss requiring a hearing aid.

Ninety percent of patients with group B *Streptococcus* meningitis survived, with one survivor showing moderate sequelae (moderate mental retardation with microcephaly), six patients with mild problems, and three patients who were completely normal (Table 7). No significant difference in outcome was noted between early and late onset of group B *Streptococcus* meningitis; however, our number of patients was small.

Of the three neonates with *S viridans* meningitis, one was completely normal on follow-up; another had moderate mental retardation, seizures, and language delay; and the third survivor attended a learning disability class

Table 3.—Outcome of Neonatal Meningitis by Birth Weight and Gestational Age

	Total No. of Patients	No. of Deaths	No. of Survivors	Sequelae		
				Normal, No.	Abnormal*	
Birth weight, g†						
<2500	13	4	9	3	Mild (4): borderline mental retardation (1), behavior disorder class (1), myopia (1), repeated a grade level (1)	Moderate (2): microcephaly (2), mild mental retardation (2), cerebral palsy (1)
≥2500	13	1	12	5	Mild (4): repeated a grade level (3), borderline mental retardation (1), hydrocephaly, IQ 85 (1)	Moderate (3): seizures (2), microcephaly (1), hydrocephaly (1), moderate mental retardation (2), myopia/amblyopia (1), sensorineural hearing loss (1)
Gestational age, wk†						
<36	9	3	6	2	Mild (2): borderline mental retardation (1), repeated a grade level (1)	Moderate (2): microcephaly (2), mild mental retardation (2), cerebral palsy (1)
≥36	17	2	15	6	Mild (5): repeated a grade level (3), borderline mental retardation (1), myopia (2), behavior disorder class (1)	Moderate (3): seizures (2), moderate mental retardation (2), mild mental retardation (2), microcephaly (1), hydrocephaly (1), myopia/amblyopia (1), sensorineural hearing loss (1)

*Numbers of patients are in parentheses.
†$P=.4$ between groups for both birth weight and gestational age.

Table 4.—Outcome of Control Group by Birth Weight and Gestational Age*

	Total No. of Patients	Sequelae		
		Normal, No.	Abnormal	(All Mild)
Birth weight, g†				
<2500	9	4	5	Visual defect (3): speech/language delay (3), minimal brain dysfunction (1), borderline IQ (1)
≥2500	12	3	9	Visual defect (5): speech/language delay (1), mild mental retardation (2), borderline IQ (1), repeated a grade level (2)
Gestational age, wk†				
<36	7	2	5	Visual defect (3): minimal brain dysfunction (1), speech/language delay (3)
≥36	14	5	9	Visual defect (5): speech/language delay (1), repeated a grade level (2), mild mental retardation (2), borderline IQ (1)

*Numbers of patients are in parentheses.
†$P=.4$ between groups for birth weight; $P=.75$ between groups for gestational age.

Table 5.—IQ Scores of Neonatal Meningitis and Control Patients*

Stanford Binet (SB) and Wechsler (W) Intelligence Scores	Meningitis Group, No. (%) (n=15)	Control Group, No. (%) (n=14)
Average		
(90-109)	8 (53)	12 (86)
Borderline		
(SB, 68-79)	3 (20)	2 (14)
(W, 70-79)	. . .	. . .
Mild retardation		
(SB, 52-67)	2 (13)	. . .
(W, 55-69)	. . .	. . .
Moderate retardation		
(SB, 36-51)	2 (13)	. . .
(W, 40-54)	. . .	. . .

*$\chi^2=4.3$, $df=1$, $P<.02$.

Table 6.—Vision, Hearing, and Language Evaluation*

	Meningitis Group		Control Group	
	No. (%) Normal	No. (%) Abnormal	No. (%) Normal	No. (%) Abnormal
Vision	12 (63)	7 (37)	13 (68)	6 (32)
Hearing	17 (89)	2 (11)	18 (95)	1 (5)
Speech/language	15 (80)	4 (20)	17 (89)	2 (11)

*Vision, $P=.75$; hearing, $P=.6$; and speech/language, $P=.4$.

Table 7.—Outcome of Early- and Late-Onset Group B *Streptococcus* Meningitis

Patient No.	Birth Weight, g	Gestational Age*	Sex/ Race	Age at Onset	Risk Factors	Age at Last Test, y	Central Nervous System	IQ (Stanford-Binet Test)	Vision	Hearing	Academics
Early											
1	2098	36	F/W	10 h	Breech/premature rupture of membranes	. . .	Died at <24 h old	. . .	. . .	. . .	. . .
2	1814	33	M/W	10 h	Premature rupture of membranes	6	Normal	. . .	Normal	Normal	Repeated 1st grade
3	2211	36	F/B	14 h	0	9	Normal	97	Myopia	Normal	97th percentile in reading and math
4	1980	35	M/B	24 h	Premature rupture of membranes	6	Normal	74	Normal	Normal	. . .
5	2440	39	F/W	4 d	. . .	1	Normal	. . .	Normal	Normal	. . .
6	2523	36	M/B	4 d	0	10	Normal	69	Normal	Normal	Repeated 1st grade
Late											
7	2892	39	F/B	9 d	0	14	. . .	107	Myopia	Normal	Repeated 7th grade
8	3062	40	F/B	14 d	Low forceps	13	Microcephaly	50	Myopia/ amblyopia	Sensorineural loss	Trainable mental handicap class
9	2778	41	F/B	17 d	Low forceps	13	Normal	94	Normal	Normal	Regular class
10	2637	41	F/B	19 d	Toxemia	7	Hydrocephaly-shunt	85	Normal	Normal	Regular class
11	2126	36	M/B	23 d	Premature rupture of membranes, amnionitis	12	Normal	83 (Cattell Test)	Normal	Normal	Behavior disorder class

*All patients' sizes were appropriate for gestational age.

Table 8.—Long-term Sequelae in Neonatal Meningitis vs Controls*

Moderate/Severe		Mild	
Meningitis (n=5)	Control (n=0)	Meningitis (n=8)	Control (n=14)
Hydrocephaly (4), shunt (3)	. . .	Mild mental retardation (2)	Mild mental retardation (2)
Microcephaly (3)	. . .	Borderline IQ (3)	Borderline IQ (2)
Seizures (3)	. . .	Mild visual defect (3)	Mild visual defect (8)
Moderate mental retardation (2)	. . .	Speech/langulage delay (4)	Speech/language delay (4)
Cerebral palsy (1)	. . .	Behavior/learning disability class (3)	Minimal brain dysfunction (1)
Moderate myopia (2)	. . .	Repeated a grade level (4)	Repeated a grade level (2)
Optic atrophy (1)	. . .	. . .	. . .
Trainable mental handicap class (1)	. . .	. . .	. . .

*Numbers of patients are in parentheses. $\chi^2=6.61$, $df=1$, and $P=.01$.

but was otherwise functionally normal. Thus, among the 15 survivors of gram-positive meningitis, five were judged as normal without any sequelae, seven had mild sequelae (borderline IQ or repeating a grade level), and three had major sequelae. Among the six survivors with gram-negative meningitis, two showed major sequelae (cerebral palsy, microcephaly, hydrocephalus seizures, and moderate visual defects), two were assessed as functionally normal, and the results of the physical and neurologic examinations of the remaining two patients followed up for less than a year were normal.

Overall, the proportion of patients among the survivors with normal outcome (38%, 8 of 21) was comparable with that in the control group. A significant difference was observed between the meningitis and control groups as to the severity of the sequelae (Table 8). Whereas 38% and 24% of the survivors of meningitis had mild and moderate to severe sequelae, respectively, 67% of the controls had mild problems and none had moderate to severe sequelae ($\chi^2=6.61$, $df=1$, $P=.01$).

COMMENT

Previous reports of the relatively rare occurrence but high mortality rate of neonatal meningitis[1-10] are confirmed in this study. Our mortality rate of 19% is lower than in most reports. This may be related to the prevalence of gram-positive infections, which have been shown to have a better prognosis, and possibly due to better supportive care as neonatal intensive care units evolved since the cited comparable studies.

In the early 1970s, group B *Streptococcus* emerged as an important cause of neonatal meningitis,[11,12] superseding *E coli* as the leading pathogen causing sepsis in infants younger than 2 months. In this study, gram-positive pathogens, predominantly group B *Streptococcus*, were isolated twice as often as gram-negative organisms, and more likely to grow from both blood and CSF cultures.

Baker and colleagues[11] observed that group B *Streptococcus* disease of early onset had a higher mortality than the late-onset type. Mulder and Zanen,[13] on the other hand, reported no difference. Our findings tend to support the observation made by Mulder and Zanen, although our number of cases is too small for definitive conclusion. Our high survival rate (90%) and the low incidence of moderate sequelae (10%) in group B *Streptococcus* meningitis are comparable with the results of other studies.[13,14]

Previous observations of a poorer outcome of gram-negative meningitis[2,6,10] are confirmed in this study, with the mortality in neonates with gram-negative infection (33%) almost three times as high as in neonates with gram-positive infections (12%). However, no significant difference was observed in morbidity rate between neonates with gram-positive and gram-negative meningitis.

It is interesting to note the co-occurrence of meningitis and sepsis in half of the neonates in the study, all of whom were symptomatic at the time the cultures were obtained. The onset of symptoms was within the first week of life in seven of the 13 neonates with concurrent meningitis and sepsis. In an earlier study of neonatal meningitis, diagnosed in our institution between 1964 and 1972, Lorch and Andrews[15] reported a similar rate of 50% co-occurrence of meningitis and sepsis.

The incidence of meningitis in our study was the same for groups with birth weights above and below 2500 g. This finding is contrary to other reports[1,3,7,16] showing greater susceptibility of low-birth-weight infants to this infection. As for the survival rate, a greater mean birth weight among survivors of this infection was observed by McCracken and Mize,[4] Hechmatt,[5] Overall,[1] and Bortolussi and colleagues.[8] A similar trend was seen in our study in which neonates of greater birth weight had a higher survival rate (92%) than neonates in the lower birth weight group (69%). A higher proportion of our patients with meningitis were girls. An almost equal white and black race distribution was observed in a general population that is two thirds black.

Past studies of neonatal meningitis by Fitzhardinge and associates,[2] Goldacre,[3] McCracken and Mize,[4] Ziai and Haggerty,[9] and Farmer and MacArthur[17] have shown CSF leukocyte count and protein concentration to be of value in predicting survival; mean CSF leukocyte count and protein concentration were significantly greater in those who died than in those who survived. Fitzhardinge and associates[2] confirmed that CSF and protein concentration, but not CSF leukocyte count or glucose values, were predictive of survival. In our study, a higher survival rate was also noted in patients with a CSF leukocyte count of less than 1000/mm^3 and protein concentration less than 5 g/L in those with higher values. However, the difference did not reach statistical significance. Variations in treatment regimens given during the 10-year study period made it difficult to analyze the influence of antibiotic therapy on outcome.

Results of the study by Fitzhardinge and associates[2] on neonates with meningitis born a decade earlier than our study patients showed a mortality rate of 44%, and only 28% of survivors were completely free of abnormalities. Seventy-two percent (13 of 18) had some positive findings, with eight of the 13 described as functionally abnormal because of impaired intelligence, and five of the 13 performing normally at home or at school. As to etiology, Fitzhardinge and associates also reported a high proportion of gram-positive pathogens (35%). In our study, with an even higher proportion of gram-positive pathogens (65%), the mortality rate was much lower (19%), but our long-term morbidity rate showed only a slight improvement.

SUMMARY

This study showed that the incidence of long-term sequelae of neonatal meningitis was comparable with that of sequelae in other high-risk neonates without meningitis, but the abnormalities in the meningitis group were more severe. However, compared with past studies, less severe sequelae were observed among our survivors of meningitis with none requiring institutional care and all attending school. Our study showed that the CSF leukocyte count, protein concentration, and glucose values were not predictive of survival.

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Reference: 1. Walson PD et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17

INDICATIONS AND USAGE: Pedia-Profen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: Pedia-Profen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **Pedia-Profen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Pedia-Profen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **Pedia-Profen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **Pedia-Profen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **Pedia-Profen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Meaningful (3 times the upper limit of normal), elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with **Pedia-Profen**. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), **Pedia-Profen** should be discontinued.

Safety and efficacy of **Pedia-Profen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **Pedia-Profen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: Pedia-Profen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—orange, berry-vanilla flavored

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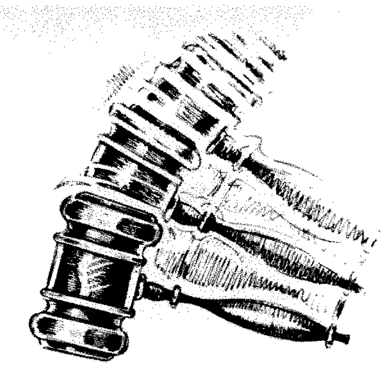

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1. Data on file, SmithKline Beecham Pharmaceuticals.

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ceuticals literature or *PDR*. The following is a brief summary.

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics.

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage and Administration: The *Augmentin* 250 mg tablet and the 250 mg chewable tablet do *not* contain the same amount of clavulanic acid (as the potassium salt). The *Augmentin* 250 mg tablet contains 125 mg of clavulanic acid, whereas the 250 mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the *Augmentin* 250 mg tablet and the 250 mg chewable tablet should *not* be substituted for each other, as they are not interchangeable.

Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* 250 mg tablets are not equivalent to one *Augmentin* 500 mg tablet. Therefore, two *Augmentin* 250 mg tablets should not be substituted for one *Augmentin* 500 mg tablet for treatment of more severe infections.

Dosage: Adults: The usual adult dose is one *Augmentin* 250 mg tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* 500 mg tablet every eight hours.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and lower respiratory tract infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Severe infections should be treated with the higher recommended dose.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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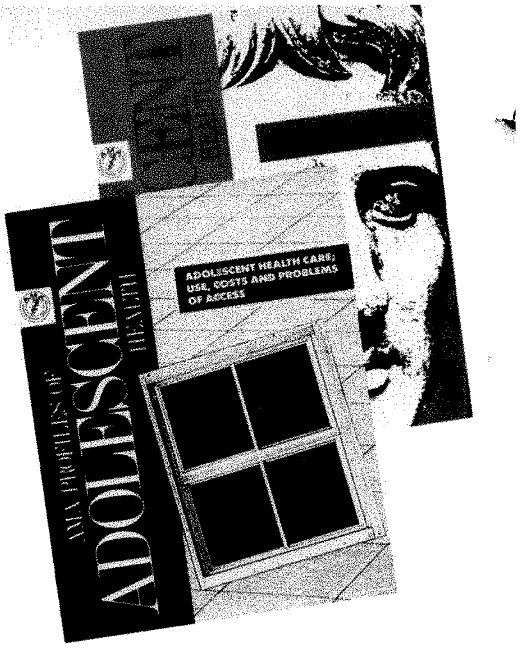

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Factors Influencing the Choice of a Residency Training Program

A Student's Perspective

Carol Carraccio, MD, Jack Gladstein, MD

• Current trends in pediatric residency training have shown that a growing number of programs have been unable to fill their available positions through the National Resident Matching Program, Evanston, Ill. This has caused a competitive climate among programs to attract medical students as potential residents. The purpose of this study was to learn what factors are important to all students in determining the rank order of the residency training programs to which they have applied. Analysis of data obtained from 600 survey respondents (40%) showed that program curriculum was most important. Factors, such as night call and benefits, took on much less importance. Differences did exist between students who applied for pediatric vs other residencies. The balance between primary and tertiary care and a university setting are examples of variables that had a greater influence on aspiring pediatricians. This information has important implications for training program directors.

(*AJDC.* 1992;146:577-580)

During the 1980s, the number of pediatric positions that was available through the National Resident Matching Program (NRMP), Evanston, Ill, showed a steady increase.[1,2] The number of these available positions, however, that was filled by US medical school graduates showed a parallel increase only through 1985. Beginning in 1986 and continuing through 1991, there has been a steady decline in the number of available positions that was filled through the NRMP. In 1991, 1493 (66%) of the 2255 positions offered by the categoric pediatric training programs that were participating in the NRMP were filled, leaving more than half of accredited pediatric training programs with unfilled positions[3]

This situation has created a competitive climate among pediatric training programs. A survey of pediatric program directors showed that the size of the training program and the availability of part-time residency positions correlated positively with the ability to fill through the NRMP.[4,5] The night call schedule and benefit package offered by the programs had no measurable impact on the ability to match.[5]

The purposes of this study were (1) to learn what factors determine senior medical students' rank order of residency training programs and (2) to determine if these factors are different for students who are entering pediatric training as compared with medical students who are pursuing other specialties.

MATERIALS AND METHODS

A mailing list of 1690 senior medical students in the South Atlantic region of the United States (including Maryland, the District of Columbia, Virginia, West Virginia, Georgia, North Carolina, South Carolina, Florida, and parts of Pennsylvania and New Jersey) was obtained from the American Medical Student Association, Reston, Va. A survey was sent to each student at the time that interviews for residency positions were being completed (January 1991). We sought sociodemographic information, specialty interest, and when in one's career the specialty choice was made; the survey was anonymous. The questionnaire consisted of a list of 25 variables (Table 1) that were chosen by the authors based on their own experience of interviewing applicants for pediatric level 1 positions, as well as on the applicable medical literature.[6-9] The study variables could be divided into the following categories: (1) quality of life (ie, geographic location, salary); (2) quality of program (ie, academic reputation, curriculum); (3) nature of the program (ie, size, volume of patients); (4) personal impression (ie, personal attention to applicant, interviews); and (5) outside influences (ie, adviser or peer recommendation). The students were asked to weigh, on a Likert scale, how these different factors influenced their choice of residency training programs. The Likert scale ranged from 0 to 5, with 0 indicating that the particular factor had no influence on the rank order of residency training programs while 5 had a great degree of influence. With the use of the same scale, the students were also asked to respond to how much impact a significant other had on their own decision and how much the fol-

Department Editors.—*Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC*

Purpose.—*This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.*

Accepted for publication November 15, 1991.

From the Department of Pediatrics, University of Maryland School of Medicine, Baltimore.

Reprints not available.

Table 1.—Senior Students' Mean Ratings of Variables Related to the Selection of Residency (n=600)

Variable	Mean	SD	Mode
Quality of faculty	4.39	0.86	5
Impression during interview	4.37	0.98	5
Quality of house staff	4.15	1.00	5
Location	4.08	1.09	5
Academic reputation	4.03	0.98	4
Spectrum of pathology	3.94	1.00	4
Patient mix	3.78	1.07	4
Personal attention	3.72	1.26	4
Volume of patients	3.59	1.09	4
University program	3.59	1.66	5
Postgraduate opportunities	3.49	1.48	4
Ancillary support	3.41	1.21	4
Program size	3.14	1.23	4
Night call	3.08	1.38	3
Primary/tertiary balance	3.08	1.56	4
Strength of a subspecialty	2.87	1.66	4
Conferences	2.84	1.30	3
Physical plant	2.84	1.40	3
Adviser recommendation	2.79	1.49	4
Peer recommendation	2.69	1.47	3
Prior match success	2.62	1.62	4
Benefits	2.41	1.39	3
Research	2.33	1.51	3
Salary	2.15	1.43	3
Brochure	1.92	1.32	3

Table 2.—Sociodemographic Characteristics and Career Choices of Responding Senior Medical Students*

Sociodemographic choices
- Mean age, 27.8 y
- Male gender, 60%
- Married, 52%
- Dependents
  - None, 77%
  - 1-2, 18%
  - 3+, 5%

Career choices (n=600)
- Internal medicine, 103 (17) [34]
- Pediatrics, 93 (15) [10]
- Family practice, 85 (14) [10]
- General surgery/
  surgical subspecialties, 101 (17) [21]
- Psychiatry, 35 (6) [5]
- Anesthesia, 32 (5) [2]
- Radiology, 30 (5) [2]
- Emergency medicine, 15 (3) [3]
- Medicine-pediatrics, 7 (1) [. . .]
- Missing/undecided, 99 (17) [. . .]

*Numbers in parentheses indicate percentages of students in our sample (n=600) who were interested in particular specialties; numbers in brackets, percentages of total National Resident Matching Program positions (n=12 985) that were filled by US graduates by specialty[10]; ellipses, data not available.

lowing four factors influenced their significant other's input into their own decision-making process: (1) geography, (2) salary, (3) night call schedule, and (4) the career opportunities for the significant other. Additional variables, not addressed by the authors, were also solicited. The first mailing was sent at the time that most students were completing their rank order list for the NRMP. There were two subsequent mailings to the same sample of students with 4-week intervals between each.

All data were analyzed with the use of the Statistical Analysis System. Nominal data were analyzed with the use of a χ^2 test or Fisher's Exact Test for two-by-two tables Numeric data were analyzed with the use of the Wilcoxon Rank-Sum test. Factor analysis was performed on all 30 variables that had scores of 0 to 5 with the use of the principal component method. A VARIMAX rotation was used to accentuate factor loadings. Logistic regression determined which rotated factors were significant for the selection of pediatric programs. A factor analysis with VARIMAX rotation was done on the two subsets of data (pediatric vs nonpediatric) to determine if selection criteria differed between the two groups.

RESULTS

The response rate for the three mailings was 40%, with 600 of the 1690 questionnaires being completed and returned; 62 could not be forwarded.

Sociodemographic characteristics and career choices of respondents can be seen in Table 2. With the exception of internal medicine, our sample fairly represented the career choices of US medical students. Students who were interested in internal medicine represented 17% of survey respondents, while 34% of the total number of positions that was filled through the NRMP by US graduates were in internal medicine.[10]

Sixty-one percent of students had given serious consideration to entering their given field before their junior clerkship in that particular area. The actual decision to enter the field was made during the first 2 years by 21% of students, during the third year by 50%, and during the fourth year by 25%.

The relative importance of each of the survey variables in selecting a residency training program is shown in Table 1. The first 10 items in Table 1 had the highest means, coupled with the smallest SDs and highest modes. Seven of these 10 variables dealt with programmatic issues, two with the interview, and the other with geographic location. Interestingly, life-style issues, such as night call, benefits, and salary ranked 14th, 22nd, and 24th, respectively. The influence of the significant other and the impact of location, job opportunities, salary, and night call on the significant other's input into the decision-making process were thought to be of little importance, with means ranging from 0.81 to 2.13, SDs ranging from 1.29 to 2.21, and modes of 0.

Since our primary interest was to understand what motivates students to choose one pediatric training program over another, we opted to use the sample of students who were interested in pediatrics as our "gold standard" and compare all others with this group. The profile of the aspiring pediatricians differed significantly from that of the other students: pediatricians were younger (26.8 vs 27.9 years, $P<.04$), female (65% vs 35%, $P<.0001$), and had fewer dependents ($P<.01$). There were 13 dependents among the 26 males vs seven dependents among the 62 females who were applying in pediatrics for whom this information was available. There was no significant difference in marital status or influence of the significant other in the decision-making process for those

Table 3.—Importance of Variables in Training Program Selection: Comparison of Students Seeking a Career in Pediatrics vs a Nonpediatric Career

Variable	P
More important to students applying to pediatric residencies vs students not applying in pediatrics	
Program is university based	<.0002
Balance between primary and tertiary care	<.001
Size of the program	<.001
Prior success in the match	<.01
Adviser recommendation	<.01
Personalized attention during interview	<.02
More important to students applying to other than pediatric residencies vs students applying in pediatrics	
Strength of a particular subspecialty	<.005

Table 4.—Clustering of Variables by Factor Analysis: Comparison of Importance to Students Applying in Pediatrics vs Other Fields

Variable
Factor 1*
Location
Job opportunities
Input into decision
Night call
Salary
Factor 2
Salary
Benefits
Night call
Ancillary support
Factor 3
Fellow/practice opportunities
Research
University setting
Subspecialty strength
Academic reputation
Factor 4†‡
Patient mix
Spectrum of pathology
Patient volume
Factor 5†‡
Quality of faculty§
Quality of house staff‡
Interview impression‡
Personal attention‡
Factor 6†‡
Primary/tertiary balance
Brochure
Prior match success
Factor 7†‡
Peer recommendation
Adviser recommendation
Factor 8
Physical plant
Program size
Factor 9
Location

*Applicable to significant other.

†Significant difference for students who were applying in pediatrics.

‡More important to students who were applying in pediatrics.

§More important to students who were not applying in pediatrics.

students who were applying in pediatrics vs other specialties. When comparing the relative importance of the factors that could potentially influence the choice of a training program between those who were interested in pediatrics vs those who were not interested in pediatrics, a significant difference was found for seven of the 30 variables that were tested (Table 3). The following factors were significantly more important to pediatricians: university setting, balance between primary and tertiary care, size of the program, prior success in the match, adviser recommendation, and personalized attention during the interview. Only the strength of a particular subspecialty was more important to students who were not applying in pediatrics. For all other areas, significant differences between groups were not detected.

Factor analysis was performed on all variables, resulting in nine clusters. A VARIMAX rotation was used to accentuate the factor loadings (Table 4). Factor 1 grouped all variables that dealt with the significant other's influence in the decision-making process. Factor 2 encompassed all the quality of life issues. Factors 3 through 6 all addressed programmatic issues. Factors 7, 8, and 9 focused on outside influence, extrinsic features of the program, and geographic location, respectively. Logistic regression demonstrated significant differences between students who were applying in pediatrics and those who were applying in other fields for four of these nine factors (Table 4). Those students who were interested in pediatrics rated the items that were contained within two of the four factors that addressed programmatic issues as more important than the students who were not interested in pediatrics. For another of the remaining two factors that dealt with program content, only the issues that concerned quality of house staff and personal attention during the interview process were more important to students who were applying in pediatrics; quality of faculty and general impression during the interview were more important to students who were not applying in pediatrics. The factor that focused on outside influence was also more important to students who were interested in a pediatric career.

In response to the request for additional items, not listed in the survey, a total of 326 additional items were identified. Twenty-eight percent dealt with life-style and family issues, 24% with programmatic issues, and another 20% addressed characteristics about the residents and faculty. An example of the most frequently cited variables within each of these three categories was cost of living, pass rate of residents who were taking Board Examinations for specialty certification, and relationships among house staff themselves and their relationship to the faculty, respectively.

COMMENT

The rank order of residency training programs, listed by our sample of students who were participating in the NRMP, appeared to be influenced most by programmatic issues. With the exception of geographic location, relative priority was assigned to academic issues over life-style.

These findings are in keeping with the work of Simmonds et al[9] who studied similar variables in a smaller population of medical students who were graduating from a single institution. Our data also support findings from a recent study on the relationship between the ability to match through the NRMP and characteristics of the program; the ability to match was associated with the addition of fewer benefits.[5] Thus, it appears that program directors may be erroneously expending time, money, and energy to improve their benefit package in the hope of enhancing resident recruitment.

Focusing on the group of students who applied in pediatrics shows a significantly higher number of women than in the group that was not interested in pediatrics. This is in keeping with the data of Rowley et al[11] that showed that the specialties with the largest proportion of women residents were public health (57.9%), combined internal and emergency medicine (54.4%), pediatrics (54.3%), and forensic pathology (53.6%). Interestingly, there were significantly less dependents in the group of students who chose pediatric careers. It may be that women choose to postpone childbearing until later in their training; hence, a larger number of women in a group may be associated with less dependents. The finding of more dependents among the males than the females within the group that was interested in pediatrics supports this explanation.

Significant differences in the importance of several factors were found between students who were applying in pediatrics and those who were applying in other fields (Table 3). Training in a university-based program was more important to students who were seeking pediatric residencies than other types of training. The type of training available in community hospitals for pediatrics vs adult medicine may have some bearing on this. The former is generally oriented to primary care with referral to university-based childrens' centers and childrens' hospitals for more specialized care, while the latter experience tends to provide all but the most specialized services that negate the need for most referrals. Also, the size of pediatric services differs from adult services in a community setting. There are generally fewer full-time pediatric faculty which may impact negatively on the teaching and academic reputation of the community program. Furthermore, the large subset of students who were pursuing family practice careers within the group of students who were not applying in pediatrics may have skewed the results. In the study by DiTomasso et al[6] that looked at factors that influenced program selection among family practice residents, they found a mean of 3.5 (scale of 1 through 5, with 1 being not important and 5 being extremely important) for importance of a community hospital setting. Program size would similarly be related to the above issue since community training programs tend to be much smaller than university-based or childrens' hospital programs. For reasons that are not well understood, pediatricians tend to attach more importance to personal attention during the interview process and the impressions of others (ie, adviser and prior match success). Strength of a particular subspecialty had more influence on those students who were not interested in pediatrics, possibly because that group included nonprimary care-oriented fields, such as surgical subspecialties.

The clustering of variables that resulted from factor analysis is similar to our initial grouping of study variables (ie, quality of life, quality of program, etc) with the following two exceptions: (1) geographic location is a separate factor and is not included with other life-style issues, and (2) three factors constitute the variables with regard to program quality. Why three of the four factors (Table 4) that dealt with programmatic issues and the factor that addressed outside influences were significantly different for those students who were applying in pediatrics vs those students who were applying in other fields is purely speculative. The literature in this area is lacking; research is needed to define further why these differences exist. It is possible that students who enter the field of pediatrics are more sensitive to humanistic issues so that variables, such as personal attention during the interview and recommendations of colleagues, hold more importance for them than students who are not applying in pediatrics. This same reasoning may also be applicable to the patient population issues (factor 4). One of the motivations for becoming a pediatrician may be to help the children with the greatest needs (ie, low socioeconomic status, those with severe illness).

Twenty-five percent of students did not make a definitive career choice until their fourth year of medical school. This finding substantiates the work of Adler et al[12] that showed that career changes occurred often in the third year of medical school, leaving faculty significant opportunity to influence career decisions of students.

The weaknesses of the study are twofold: (1) the response rate to the survey was 40%, and it is unclear why it was not greater; and (2) the questionnaire was not pretested so information with regard to reliability and validity is not available. Several important conclusions emerged, however. With the exception of geographic location, academic issues take precedence over life-style issues in determining the rank order of residency training programs. Differences do exist between the group of students who apply in pediatrics vs those who seek other careers, with certain programmatic issues and the impact of outside influence being more important to aspiring pediatricians. This information may be helpful to faculty involved in resident recruitment efforts.

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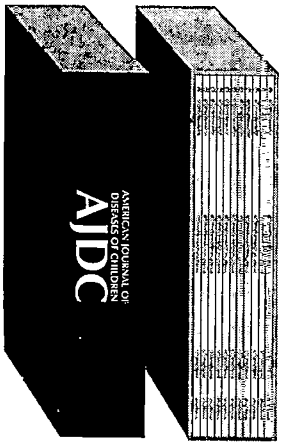

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Effect of Somatotropin of Mammalian Cell Origin in Growth Hormone Deficiency

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• Sixty-nine growth hormone–deficient patients were treated for 1 year with somatotropin (recombinant DNA-derived human growth hormone) produced in mouse cells. The growth velocity of the 50 patients (72%) in whom the effectiveness of this growth hormone could be evaluated increased from a mean (±SD) of 3.5±1.1 to 8.7±1.6. cm/y. An enhanced rate of weight gain was also observed. Bone age was not unduly accelerated. One of 66 patients developed antibodies to recombinant growth hormone, which did not affect the response to therapy. No patient developed antibodies to host cell proteins. An increased insulin response to a standard glucose load, without any change in glucose tolerance, was observed after 1 year of treatment. This authentic sequence human growth hormone preparation produced in mammalian cells is both effective and safe in the treatment of children with growth hormone deficiency.

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The development of recombinant DNA technology has led to a variety of methods that allow expression of the human growth hormone (hGH) gene in several cell lines, both prokaryotic[1,2] and eukaryotic.[3,4] Large-scale production of methionyl human growth hormone (hGH-met or somatrem) in *Escherichia coli* was followed by clinical trials of this preparation in children with growth hormone deficiency in several countries.[5-8] The generally favorable results, coupled with the association of several cases of Creutzfeldt-Jakob disease and pituitary growth hormone therapy,[9] led to the licensing of hGHmet for use in the treatment of growth hormone deficiency. Advances in technology and modifications in the production process[10,11] have resulted in the availability of authentic sequence (methionine-free) recombinant somatotropin (recombinant human growth hormone [hGHr]) also produced in *E coli.* This material has undergone several clinical trials[8,12-15] and is now also available for the treatment of patients with growth hormone deficiency.

Authentic sequence hGHr has also been produced in mammalian cells. In the study to be described, the growth hormone used was produced by introducing the hGH-N gene into a cell line (C-127) derived from mouse mammary adenocarcinoma.[16] An incomplete bovine papillomavirus was used as a vector. DNA is present in this hGHr in concentrations below 0.1 pg/IU, which is significantly less than the standard permitted by the Food and Drug Administration for DNA in recombinant products of 10 pg per dose. Vector DNA, oncogenes, or oncogene proteins are not detectable in this preparation.[17] The vector DNA does not code for virus replication or viral capsid protein production. Recombinant hGH is secreted into the medium of mammalian cells in which transformed cells are grown, and is harvested without cell disruption. This report presents data on the effectiveness of this hGH preparation, produced in mammalian cells, in the treatment of 50 children with growth hormone deficiency observed for a period of 12 months. Safety data are presented on all 69 patients who initially began therapy.

MATERIALS AND METHODS

Patient Population

All patients met stringent criteria for inclusion in the study. They had reached their fourth birthday and were prepubertal when treatment was begun. Pretreatment growth velocity was less than 4.5 cm/y and/or less than the 10th percentile for age.[18,19] Height was greater than 3 SDs[19,20] below the mean for age in patients with idiopathic growth hormone deficiency. Bone age[21,22] was delayed more than 1 year and/or 1 SD below the mean for age in patients younger than 5 years or delayed more than 2 years and/or 2 SDs below the mean for age in older children. Height and bone age criteria were not applied to patients with organic growth hormone deficiency. All patients were euthyroid, with or without levothyroxine sodium therapy, when tested for growth hormone deficiency. The peak serum growth hormone concentration in response to at least two provocative tests was 8.0 ng/mL or less, as measured in the laboratory usually used by each investigator. Acceptable stimuli were insulin-induced hy-

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poglycemia,[23] oral levodopa,[24] intravenous arginine hydrochloride,[25] oral clonidine hydrochloride,[26] and parenteral glucagon.[27] A total of 152 studies were performed in 69 patients. Insulin-induced hypoglycemia was used as a stimulus in 46 tests, levodopa in 38 tests, arginine in 37 tests, clonidine in 23 tests, and glucagon in eight tests. There was no evidence of any nonendocrine condition that could interfere with growth. Patients had not received prior therapy with somatotropin or somatorelin (growth hormone–releasing hormone). They had not been given anabolic steroids in the previous 3 years.

Sixty-nine children with growth hormone deficiency from 21 clinical centers began treatment. Each patient had been followed up by the same investigator for at least 6 months before growth hormone therapy was begun. Measurements were performed using the same stadiometer for each patient before treatment and throughout the 12 months of growth hormone administration. All patients were studied under a common protocol approved by the human subject protection process at each participating institution. Evidence of approval, as well as signed informed consents, are on file at Serono Laboratories, Norwell, Mass.

Children ranging in age from 4.09 to 14.90 years began treatment. The majority were male (50 [72%]) and 48 (70%) had idiopathic growth hormone deficiency. Forty-four patients (64%) had isolated growth hormone deficiency. In addition, 12 patients had thyrotropin deficiency; six patients were deficient in growth hormone, thyrotropin, and corticotropin; two patients had growth hormone and antidiuretic hormone deficiency; two patients had growth hormone, thyrotropin, and antidiuretic hormone deficiencies; two patients were deficient in growth hormone, thyrotropin, corticotropin, and antidiuretic hormone; and one patient was deficient in growth hormone and corticotropin. All patients, with the exception of the last-mentioned individual, who did not receive glucocorticoid replacement, received standard replacement medications for the additional deficiencies. During growth hormone therapy, the dose of levothyroxine sodium did not exceed 5 ug/kg per day or a total of 150 ug/d. The dose of glucocorticoid was limited to 15 mg/m^2 per day of hydrocortisone or its equivalent.

Sixty-seven patients completed 12 months of therapy. One patient had discontinued treatment at 6 weeks when he developed symptoms of spinal cord compression due to intrathecal spread of a glioma, and a second patient was unavailable for follow-up after 9 months.

A total of 17 patients could not be included in the evaluation of efficacy because puberty began during treatment in five patients, the dose or duration of hGH administration did not follow the protocol in four patients, and the dose or duration of concomitantly administered medication was not within the limits set in the protocol in four patients. Review of data at the completion of 12 months of treatment indicated that four additional patients had not met the entry criteria. Thus, the efficacy of hGHr treatment could be evaluated after 12 months in 50 patients. These subjects did not differ from the total group of patients who began treatment in terms of any demographic variable.

hGHr Treatment

All patients received 0.06 mg (approximately 0.2 IU) of authentic sequence hGHr somatotropin (Saizen) per kilogram of body weight subcutaneously three times each week. At the time this study was designed, this dose was standard for several clinical trials of hGHr then under way.

Special Laboratory Procedures

In addition to the regular determination of serum electrolyte concentrations, routine chemistry studies, including liver function tests, routine hematologic studies, and standard urinalyses, several specialized studies were conducted before growth hormone therapy was begun and at specified intervals thereafter.

The serum concentration of somatomedin C insulinlike growth factor I (IGF-I) was measured before treatment and at 2, 6, and 12 months after growth hormone administration was begun. The timing of blood drawing for this determination relative to the last growth hormone injection was not standardized. A commercial assay kit (INCSTAR Corp, Stillwater, Minn), which employs a human serum extract as standard,[28] was used for this measurement.

All the patients were tested every 2 months after the initiation of hGHr therapy for the development of antibodies to hGH (anti-hGHAb) and to mammalian cell-derived peptides (anti-MCPAb) that may contaminate hGHr.

Frozen serum samples were collected at each study center and analyzed centrally at the University Children's Hospital (Freiburg, Germany) by one investigator (H.J.Z.). Anti-hGHAb levels were measured by liquid radioimmunoassay[29] using polyethylene glycol to separate bound and free hormone.[30] A serum sample was considered positive if the amount of hGH labeled with iodine 125 bound at a final serum dilution of 1:10 was greater than two times the nonspecific binding of a negative serum pool tested at the same dilution. Specificity of binding was verified through displacement with an excess of unlabeled hGH. Serum samples found to be positive for anti-hGHAb were further characterized by titration and the determination of association constant and binding capacity.

Anti-MCPAb levels were measured by an indirect enzyme-linked immunosorbent assay. Three different protein and/or peptide fractions derived from host cells not bearing the growth hormone-N gene were used as antigens; one was the crude cell lysate, and the other two were derived from this material by further purification following the standard hGH production procedure. The well walls of polystyrene microtiter plates were coated with 0.1 μg of the respective antigen or antigen pool and incubated overnight in 100 μL of serial dilutions of serum (1:8 to 1:256). Bound anti-MCPAb were visualized by horseradish peroxidase–labeled rabbit anti–human IgG antibodies using orthophenylenediamine as a substrate. Specific anti-MCPAb obtained by immunizing rabbits with each of these three antigens were used as positive controls. A serum sample was considered positive if the optical density at a serum dilution of 1:8 was more than 3 SDs above the mean value of that in negative control serum samples.

Before treatment was begun and at 2, 6, and 12 months thereafter, thyroid function was evaluated by measuring the serum concentrations of thyroxine and thyrotropin using standard methods. The concentrations of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were also measured according to standard laboratory techniques 6 and 12 months after hGHr therapy was begun. Blood was obtained for the determination of serum lipid concentrations after an overnight fast.

A standard oral glucose tolerance test was performed before growth hormone was administered and at 6- and 12-month intervals after treatment was begun. The dose of glucose was 1.75 g/kg of body weight up to a maximum of 75 g. Serum samples were obtained after an overnight fast and at a half hour, 1, 2, and 3 hours after glucose administration. Serum glucose was measured according to a standard technique and serum insulin was measured with a solid phase assay using a commercial kit (Immophase, Corning Medical, Medfield, Mass).

Analysis of Data

Pretreatment growth velocity was annualized from the change in height observed for a period of 6 to 12 months before growth hormone treatment was begun. The treatment growth velocity was based on the observed change in height for a period of 12 months of growth hormone treatment. Pretreatment weight change and a change of weight while receiving growth hormone treatment were determined in the same fashion. The SD scores (ie, the number of SDs from the mean) for height and weight were calculated using the formula published by Tanner et al[31] and the data from the National Center for Health Statistics.[20] The

Table 1.—Effect of Recombinant Human Growth Hormone (hGHr) of Mammalian Cell Origin on Growth and Weight Gain*

	Pretreatment	12 mo
Growth (n=50)		
Growth velocity, cm/y	3.5±1.1	8.7±1.6
Growth velocity SD score for chronologic age	–2.9±1.3	3.4±2.3
Height SD score	–3.6±1.1	–3.0±1.1
Weight (n=47)		
Weight gain, kg/y	1.6±1.8	3.6±1.5
Weight SD score	–2.3±0.9	–2.0±0.9

*Values are means±SDs. *P*<.0001 by paired *t* test for all differences.

Table 2.—Effect of Recombinant Human Growth Hormone (hGHr) of Mammalian Cell Origin on Serum IGF-I*

Time of hGHr Administration	Serum IGF-I, nmol/L
Pretreatment (n=69)	8.2±5.8
Posttreatment	
6 mo (n=54)	12.6±9.4†
12 mo (n=46)	16.9±9.7†

*Values are means±SDs. IGF-I indicates insulinlike growth factor I.
†*P*<.0001 when compared with pretreatment.

SD scores for height velocity for chronologic age was calculated using the British data of Tanner et al.[16]

The change in bone age was derived from blind readings of bone age films (C.R.R.) obtained before growth hormone therapy was begun and at the end of 12 months of treatment. Pretreatment and treatment films were read simultaneously. The change in bone age was compared with the change in height age[20] during a period of 1 year of therapy. Growth velocity, growth velocity SD scores for chronologic age, height SD scores, weight gain and weight SD scores before growth hormone administration and after 12 months of therapy were compared using a paired *t* test against a null hypothesis of no difference between the two time points.[32] Similar comparisons were made for the mean serum concentrations of somatomedin C, thyroxine, thyrotropin, lipids, and the blood glucose and insulin response to glucose loading.

RESULTS

Effect on Growth and Weight Gain

As shown in Table 1, treatment with this hGHr preparation for 12 months significantly increased growth velocity and growth velocity SD scores for chronologic age, as well as height SD scores in these 50 prepubertal children with growth hormone deficiency. There was also a significant increase in the rate of weight gain and weight SD scores. There was clear catch-up in both height and weight.

Effect on the Serum Concentration of IGF-I

As shown in Table 2, the administration of hGHr resulted in a significant increase in the serum concentration of IGF-I. This change was present at both 6 and 12 months after therapy was begun.

Effect on Bone Age

The bone age advanced at a rate slightly less than the change in height age for a period of 1 year of therapy with hGHr. The change in height age was a mean (±SD) of 1.4±0.3 years. The change in bone age was 1.3±1.0 years when interpreted by the Greulich and Pyle[21] method and was 1.2±0.9 years when interpreted by the Tanner-Whitehouse method.[22] The ratio of change in bone age to change in height age was 0.9±0.8 and 0.9±0.7, respectively, when bone age was read by these two methods. Although there was wide variability in the change in bone age during treatment, the mean change was consistent with no undue acceleration in bone age in response to hGHr treatment.

Immunogenicity of hGHr

Antibodies to hGH were detected in only one of 66 patients from whom serum samples were available during a period of 1 year. This patient could not be included in the evaluation of efficacy because he received excessive glucocorticoid replacement with prednisone, equivalent to 25 mg of hydrocortisone/m^2 per day, during the first 6 months of therapy. In that time, he grew 0.6 cm (1.2 cm/y). Antibodies were first noted at 2 months and persisted in all additional serum samples obtained during 12 months of treatment. After 2 and 4 months of treatment, antibody titers of 1:10 and 1:30, respectively, were too low for further analysis. Increasing titers of antibodies were found in the subsequently obtained serum samples. However, even in the 12-month sample, they exhibited a low apparent association constant (9.7 × 10^8 L/mol) and binding capacity (0.15 mg/L). These antibodies did not neutralize the effect of hGHr. Growth was not attenuated in this patient as shown by an annualized growth velocity of 11.4 cm/y during the second 6 months of treatment when glucocorticoid replacement had been changed to 12.5 mg of hydrocortisone/m^2 per day.

Antibodies to host cell proteins were not found in any patient during the year of growth hormone treatment.

Effect on Thyroid Function

Twenty-one (31%) of the 67 patients who completed 12 months of treatment had central hypothyroidism before hGHr administration was begun and were receiving replacement therapy with appropriate dosages of levothyroxine. Thus, 46 patients were at risk of developing hypothyroidism during the 12 months growth hormone was given. Four patients (8.7%) were judged to have become hypothyroid while receiving hGHr because they developed subnormal serum thyroxine concentrations.

Effect on Glucose Tolerance and Insulin Secretion

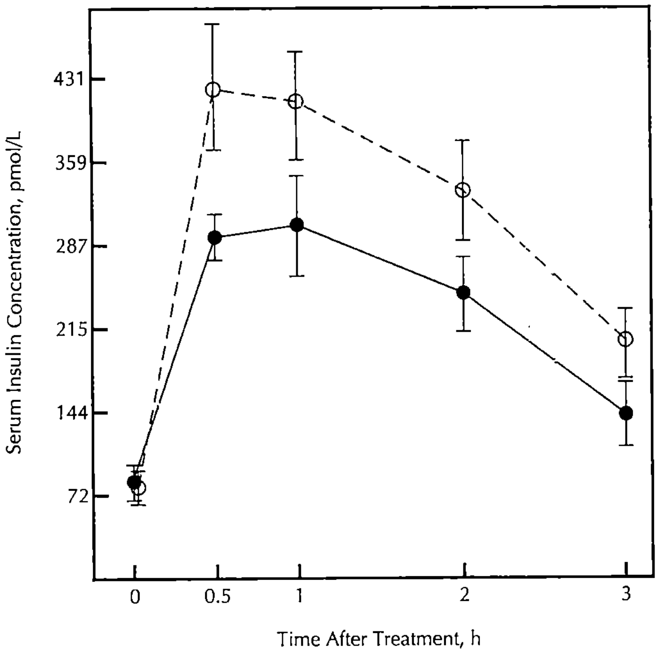
Glucose tolerance did not change after 12 months of growth hormone therapy. As shown in Table 3, there was no change in the blood glucose concentration at any of the times sampled after an oral glucose load at the end of 1 year of treatment. While the mean values at each time of sampling are lower at 12 months than before treatment, these differences are not statistically significant (*P*>.05).

The effect of 12 months of hGHr treatment on insulin secretion in response to an oral glucose load is shown in the Figure. There was a statistically significant (*P*<.05) increase in the serum concentration of insulin through 2

Table 3.—Effect of Recombinant Human Growth Hormone (hGHr) of Mammalian Cell Origin on Glucose Tolerance*

Time After hGHr Treatment, h	No. of Patients	Blood Glucose, mmol/L	
		Pretreatment	12 mo
0	63	4.8±0.8	4.4±0.8†
0.5	60	8.3±2.0	7.8±2.4
1	64	7.6±2.6	7.1±1.8
2	64	6.5±1.6	5.0±1.2
3	61	4.8±1.5	5.0±1.3

*Values are means±SDs.
†$P>.05$.



Mean (±SE) serum insulin concentrations in response to an oral glucose load before (solid circles) and after (open circles) 12 months of somatotropin therapy. Differences are significant ($P<.02$) at 0.5 hour, 1 hour, and 2 hours.

hours after glucose administration at the end of 12 months of growth hormone treatment.

Insulin concentrations in excess of 718 pmol/L at one time point in response to glucose loading were observed in 15 (22%) of the 67 patients who completed 1 year of treatment. In 10 patients, there were two or more consecutive insulin values in excess of 718 pmol/L during 12 months of growth hormone administration.

Two of these 10 patients were massively obese. One patient had septo-optic dysplasia, multiple pituitary hormone deficiencies, and acanthosis nigricans, and the second patient underwent surgery and radiation for a craniopharyngioma and also had multiple pituitary hormone defects. Of the remaining eight patients who developed hyperinsulinism, weight exceeded the 90th percentile for height in five patients and obesity may have played a role in their insulin resistance. In the remaining three patients, there were no obvious factors contributing to the elevated insulin concentrations other than hGHr treatment.

Table 4.—Effect of Recombinant Human Growth Hormone (hGHr) of Mammalian Cell Origin on Serum Lipids*

	Serum Lipid Concentrations, mmol/L	
	Pretreatment	12 mo
Cholesterol	5.3±1.0 (69)	4.8±1.1 (66)†
Triglycerides	0.9±0.6 (69)	1.0±0.6 (65)
High-density lipoprotein cholesterol	1.6±0.3 (67)	1.5±0.3 (62)‡
Low-density lipoprotein cholesterol	3.3±0.9 (66)	2.8±1.0 (56)§

*Values are means±SDs (n).
†$P<.0001$.
‡$P<.004$.
§$P<.0004$.

Effect on Serum Lipids

As shown in Table 4, the administration of hGHr for 12 months significantly lowered total serum cholesterol concentration as well as both high-density lipoprotein and low-density lipoprotein cholesterol concentrations. There was no effect on triglyceride concentrations.

COMMENT

These results clearly show the efficacy of hGHr of mammalian cell origin in the treatment of the growth failure that occurs in children with growth hormone deficiency. The response is comparable to that previously reported with hGHr preparations, both with[5-8] and without[8,12-15] a terminal methionine, produced by the genetic engineering of *E coli.* The effect on weight and the rate of weight gain is also comparable to that observed in these previously reported studies. These effects were associated with the expected increase in the serum concentration of IGF-I (somatomedin C) that persisted through 12 months of growth hormone administration. A similar increase in IGF-I has been noted in patients receiving hGHr of bacterial cell origin.[5]

The bone age advanced at a rate that exceeded the change of chronological age, but was comparable to the advance in height age. Thus, there was no undue acceleration in bone age during this initial 12 months of therapy. Review of those studies of hGHr therapy where bone age advance is considered showed comparable changes. Kaplan et al[5] reported a change in bone age in advance of the change in chronologic age in treated patients, as did Milner et al.[7] In both of these studies, there was catch-up growth in height without any undue acceleration in bone age.

The immunogenicity of this hGHr preparation was extremely low. Only one (1.5%) of 66 patients developed antibodies that bound labeled hGH. Early preparations of hGHmet were highly immunogenic and contaminated with *E coli* proteins. Antibodies to hGHmet were detectable in between 60%[8] and virtually 100%[5,13] of treated patients. However, growth attenuation, presumably associated with anti-hGH antibodies, has been uncommon.[5,33] Currently used preparations of hGHmet or authentic hGHr of bacterial cell origin are much less immunogenic, and the reported prevalence of antibodies to these preparations has varied from none[13] to 9.5%,[12] with most series reporting antibodies in less than 5% of patients.[8,13-15,34]

The immunogenicity of hGHr derived from genetic engineering of mammalian cells was found to be equally low, and growth attenuation did not occur in the only patient who developed antibodies in our study.

The development of hypothyroidism in four patients (8.7%) who were at risk for this occurrence during growth hormone therapy is comparable to the prevalence observed with hGHmet[5] and is well within the wide range of incidence observed in various studies in which children were treated with human pituitary growth hormone.[35] There appears to be no change in the incidence of hypothyroidism developing during treatment with hGHr of mammalian cell origin.

While glucose tolerance was not significantly altered with 12 months of treatment with hGHr, hyperinsulinism was observed at each time sampled during a 3-hour oral glucose tolerance test. Comparable hyperinsulinism and insulin resistance was not seen during the short-term administration of hGHmet to patients with growth hormone deficiency.[5] However, hGHmet treatment resulted in hyperinsulinism after 5 days of administration to girls with Turner's syndrome[36] and the induction of insulin resistance is a common effect of hGH administration.[37] Thus, this finding is expected. With the exception of the report by Kaplan et al,[5] previously published studies of hGHr treatment in growth hormone deficiency do not systematically address this issue.

The serum concentration of cholesterol and low-density lipoprotein cholesterol were both lowered during treatment. Hyperlipidemia has been observed in adults with growth hormone deficiency[38] and in some children with growth hormone deficiency.[39] Our observation of a lipid-lowering effect of hGHr is consistent with previously reported results in other series of children and adults receiving growth hormone treatments.[39-41]

Our results clearly show that hGHr produced by genetically engineered mouse cells, when administered during a period of 12 months, is effective in the treatment of children with growth hormone deficiencies. This hGHr preparation is also safe and side effects are minimal.

What are some potential risks and benefits of hGHr? The preparative method uses a tumor cell line to express hGH and a viral vector to introduce the hGH-N gene. Theoretically, this method carries a risk of transmitting potentially oncogenic DNA from the mouse tumor cell line. The amount of DNA in this preparation is extremely small and is well below the amount permitted by the Food and Drug Administration. Even if significant DNA were present, it would be extremely unlikely that any DNA-induced transformation would occur. The method also carries the risk of introducing viral material into hGHr. The virus used in introducing the growth hormone gene is incomplete and cannot replicate. Viral DNA has not been detected in the preparation. In addition, neither oncogenes nor oncogenic proteins are detectable.

Presently available hGHr preparations are expressed with *E coli* and carry the risk of contamination with *E coli* proteins. Sensitization to such proteins may be responsible for rare allergic reactions observed in selective recipients of hGHr. No such risk is seen with hGHr of mammalian cell origin. Contamination with mouse cell proteins and antibodies to mouse cell proteins pose theoretical risks to therapy with hGHr used in this study. However, no mouse cell proteins and no such antibodies have been detected. Antibodies to human growth hormone appear to be equally rare in patients receiving *E coli*– and mammalian cell-derived hGHr preparations. While a great deal of concern regarding such antibodies and their potential growth-attenuating effects accompanied the introduction of hGHr, these have proved to be unusual problems.

The addition of another safe and effective hGHr preparation to those currently available in the United States and in other countries should enhance competition and lower the costs of providing growth hormone therapy to children who can benefit from such treatment.

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(*Arch Otolaryngol Head Neck Surg.* 1992;118:401-405)

Calcium and Zinc Retention From Protein Hydrolysate Formulas in Suckling Rhesus Monkeys

Silvia Rudloff, PhD, Bo Lönnerdal, PhD

• *Objective.*—To determine calcium and zinc retention from infant formulas based on protein hydrolysates.

***Design.*—Randomized, crossover.**

***Setting.*—Newborn nursery at the California Primate Research Center, Davis.**

***Participants.*—Suckling infant rhesus monkeys (N = 7), aged 6 weeks at the beginning of the study. Each infant received seven different formulas.**

***Interventions.*—Fasted infant monkeys were fed diets radiolabeled with calcium 47 and zinc 65. Retention was determined by counting whole body radioactivity immediately after dosing and 7 days after dosing.**

***Measurements and Results.*—Retention of ^{47}Ca was a mean (±SEM) of 79%±4% from casein hydrolysate and 72%±6% from the whey protein hydrolysate formula. Calcium 47 retention from hydrolysates based on whey protein/casein mixtures (a ratio of 60:40 or 50:50) was similar despite differences in protein sources and calcium content. Calcium 47 retention from two types of soy/collagen hydrolysate formula was found to be 68%±6% and 59%±4%, respectively, which is significantly lower than retention from casein hydrolysate. Considering the different calcium content of these formulas, total calcium retention from milk protein hydrolysates was higher than from soy/collagen products. Retention of ^{65}Zn from milk protein hydrolysates ranged from 18%±3% to 29%±4% and was higher than that from soy/collagen formulas with a mean retention of 7%±3% and 10%±4%, respectively. Despite these differences in ^{65}Zn retention, total zinc retention from all soy/collagen formulas was similar due to their higher zinc content.**

***Conclusions.*—Calcium and zinc bioavailability was high from formulas based on milk protein hydrolysate, but was considerably lower from soy hydrolysates. Higher levels of calcium and zinc provided in soy hydrolysate formula compensated for the lower bioavailability and resulted in similar amounts of calcium and zinc retained.**

(*AJDC.* 1992;146:588-591)

Recently, a variety of so-called hypoallergenic or hypoantigenic formulas have been developed based on various enzymatically hydrolyzed protein sources, eg, cow's milk whey proteins and caseins and mixtures of soy protein and bovine collagen. Some products are designed for the possible prevention of allergenic reactions, others for therapeutic use. Most clinical studies to date have focused on the capacity of these products to treat infants with allergies. However, since these formulas contain different protein, mineral, and trace element levels, it is also important to evaluate the nutritional adequacy of these products.

Calcium and zinc bioavailability is still a major area of concern in infant nutrition. It is known that certain milk components have an impact on the absorption of these minerals. Proteins such as caseins and their digestive products bind calcium[1] and zinc,[2] potentially increasing their solubility, which might then enhance absorption. If, however, digestion of casein is limited, a negative effect on trace element absorption can be found.[3] Other formula components have been found to have an inhibitory effect on absorption, such as phytate in soy formulas[4,5] or unbalanced mineral formulations. High levels of calcium, for example, are thought to inhibit zinc absorption[6]; a similar effect has also been found on iron absorption.[7,8] Iron, in turn, has been reported to have a negative effect on zinc absorption.[9,10]

It is not known whether different peptides in these formulas or their respective mineral compositions affect the absorption and retention of calcium and zinc. Therefore, suckling infant rhesus monkeys were used to study the effect of several hydrolysate formulas on calcium and zinc retention. Results from this animal model have previously been shown to be highly correlated to data from comparative studies in human subjects.[11]

MATERIALS AND METHODS

The hydrolysate type, protein composition, and mineral/trace element contents of the seven formulas are given in Table 1. All formulas were supplemented with vitamin D_3 at similar levels (1.2 to 1.4 μg/dL). Formulas A (MA-1), E (Aptamil Hypoantigen), and G (Pregomin) are commercially available; the other products were experimental formulas produced in pilot plants.

All formulas were simultanously radiolabeled by the addition of 0.5 μCi of calcium 47 chloride (Amersham, Arlington Heights,

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Table 1.—Composition of Infant Formulas (per Deciliter of Reconstituted Formula)*

Contents	A Casein	B Whey	C Whey/Casein (60:40)	D Whey/Casein (60:40)	E Whey/Casein (50:50)	F Soy/Collagen (50:50)	G Soy/Collagen (50:50)
Protein, g	2.0	2.0	2.0	1.5	1.5	1.5	2.0
Minerals/trace elements							
Calcium, mg	60	60	60	40	68	64	51
Protein, mg	34.5	34.5	34.5	34.5	35	34	25.5
Zinc, mg	0.4	0.4	0.4	0.4	0.6	0.9	0.6
Iron, mg	0.9	0.9	0.9	0.9	2.0	1.6	1.7
Calcium/protein ratio	1.7	1.7	1.7	1.2	1.9	1.9	2.0
Iron/zinc ratio	2.25	2.25	2.25	2.25	3.33	1.78	2.83

*According to manufacturer's information.

Table 2.—Calcium 47 and Zinc 65 Retention From Protein Hydrolysate Formulas (as a Percentage of Dose)

Formula	^{47}Ca Retention*	^{65}Zn Retention*
A Casein hydrolysate	78.8±3.5	28.5±4.2†
B Whey hydrolysate	71.7±6.3	26.5±3.7
C Whey/casein (60:40) hydrolysate	75.0±3.5	26.4±5.1
D Whey/casein (60:40) hydrolysate	70.8±5.2	21.1±2.9
E Whey/casein (50:50) hydrolysate	68.8±3.7	17.6±3.4
F Soy/collagen hydrolysate	59.1±4.1	7.4±3.1†
G Soy/collagen hydrolysate	67.9±5.5	10.2±3.7

*Numbers given are mean±SEM.

†Statistically significant difference between formulas A and F; *P*<.01.

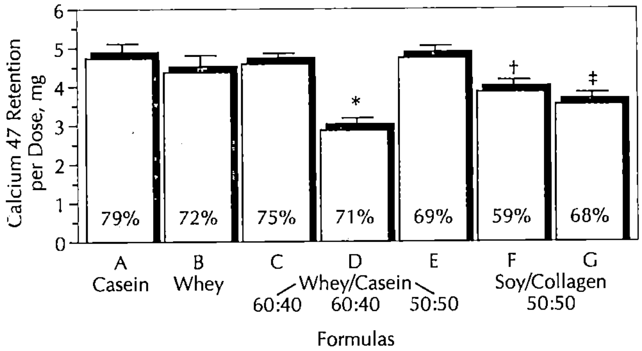

Fig 1.—*Mean±SEM calcium retention (in milligrams per 10-mL dose). Mean percentages are shown within the bars. The asterisk indicates that the retention of calcium from formula D is significantly lower than that from formulas A, B, C, E (P<.001), and F (P<.05); dagger, the retention from formula F is significantly lower than that from formulas A, C, E (P<.01), and B (P<.05); and double dagger, the retention from formula G is significantly lower than that from formulas A and E (P<.05).*

Ill) and 0.5 μCi of zinc 65 chloride (New England Nuclear Products, E. T. Du Pont, Boston, Mass) and were then allowed to equilibrate for 3 hours.[11] Because of their different energy maxima, ^{47}Ca and ^{65}Zn retention could be evaluated separately, but simultaneously.

Seven suckling rhesus monkeys (*Macaca mulatta*) from the California Primate Research Center at the University of California, Davis, aged about 6 weeks at the beginning of the studies, were housed with their mothers. Once every week, infant monkeys were separated, weighed, and fasted for 5 hours. Radiolabeled hydrolysate formulas (10-mL dose) were then given by orogastric intubation in a randomized block design. No food was allowed for 2 hours after dosing. Seven days after dosing, whole body retention of ^{47}Ca and ^{65}Zn was determined by counting whole body radioactivity, as described earlier.[9]

Isotope retention was calculated taking into account the rapid decay of ^{47}Ca and retained isotopes from previous doses. During a 3-week test period, endogenous excretion of ^{47}Ca and ^{65}Zn was found to be minimal within 7 days.

This study was approved by the Animal Care and Resources Committee and by the Radiation Safety Committee at the University of California, Davis. Statistical analysis was done by analysis of variance and the Fisher Least Significant Difference Test using a software package (StatView 512+, Brainpower Inc, Calabasas, Calif). A statistically significant difference was accepted at *P*<.05.

RESULTS

Calcium 47 retention in suckling rhesus monkeys was found to be a mean (±SEM) of 78.8%±3.8% from the casein hydrolysate formula (A) and 71.7%±6.3% from the whey hydrolysate formula (B) (Table 2). Calcium 47 retention from formula C, with a whey/casein ratio of 60:40, was 75.0%±3.5%. The difference between these formulas, however, was not statistically significant.

A lower protein content in formulas D and E, both based on hydrolyzed caseins and whey proteins, was accompanied with similar ^{47}Ca retention results, 70.8%±5.2% from formula D and 68.8%±3.7% from formula E. Calcium 47 retention from the soy/collagen formulas was found to be 59.1%±4.1% from formula F and 67.9%±5.5% from formula G, the latter having a higher protein but lower calcium content than its counterpart F.

Statistical analysis revealed a significant difference between the highest (formula A) and lowest ^{47}Ca retention (formula F) observed in this study (*P*<.01).

Total calcium retention was calculated using the calcium content of the dose (10 mL) and the retention of the radiolabel ^{47}Ca determined by counting whole body radioactivity. Thus, calcium retention (Fig 1) ranged from 4.7±0.2 mg per dose from formula A to 2.8±0.2 mg per dose from formula D, which had the lowest calcium content (Table 1). The difference between calcium retention from milk hydrolysate formulas (A through E) was statistically significant compared with the two soy/collagen formulas F (*P*<.05) and G (*P*<.01). Calcium retention from formula G was also lower than from formulas B (*P*<.05) and C (*P*<.01). The low protein concentration combined with a low calcium level in formula D led to lower calcium retention compared with all other formulas; the difference was significant for formulas A, B, C, and E (*P*<.001) and for formula F (*P*<.05), but not for formula G.

Zinc 65 retention from formulas based on milk protein hydrolysates ranged from 17.6%±3.4% (formula E) to 28.5%±4.2% (formula A); the differences among these formulas, however, were not significant. When these re-

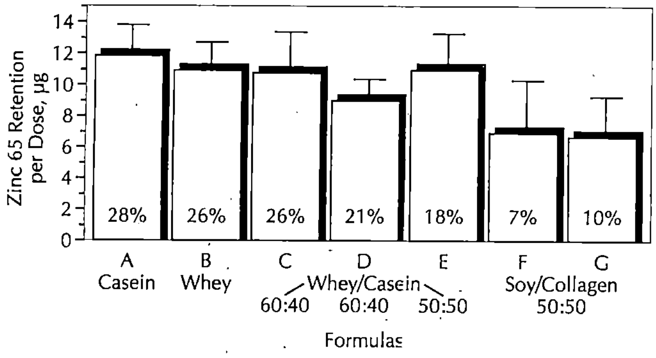

Fig 2.—*Mean±SEM zinc retention (in milligrams per 10-mL dose). Mean percentages are shown within the bars.*

sults were compared with those obtained for soy/collagen formulas, it was evident that ^{65}Zn retention from formula F (7.4%±3.1%) was lower than that from formula A (P<.001), B, C (P<.01), and D (P<.05); ^{65}Zn retention from formula G (10.2%±3.7%) was lower than from formulas A, B, and C (P<.01). These differences in ^{65}Zn retention were partly eliminated when calculating total zinc retention, due to the higher zinc content of formulas E, F, and G. Total zinc retention still appeared to be lower from formulas based on soy/collagen hydrolysates; however, the difference was not statistically significant due to the relatively large standard errors (Fig 2).

COMMENT

Calcium and zinc retention was determined by counting whole body radioactivity of suckling rhesus monkeys receiving radiolabeled hydrolysate formulas. Each infant received all products, increasing the statistical power of the study. At the beginning of a 3-week period, a single dose of ^{47}Ca and ^{65}Zn was given to determine the biological turnover of both isotopes. It was concluded that endogenous excretion within the relevant weekly period was minimal and correction for this was therefore unnecessary. This is in agreement with an earlier study on calcium retention by Bronner et al[12] and on zinc retention by Hawkins et al.[13]

Calcium 47 retention was highest from the casein hydrolysate formula (A; 78.8%±3.5%). In formulas with hydrolyzed whey proteins and caseins, calcium retention seemed to increase slightly with the proportion of casein peptides present in the formulas (Table 2). Casein phosphopeptides have been suggested to enhance calcium absorption due to their ability to increase calcium solubility in the intestinal lumen.[14-18] In this study, however, the difference between calcium retention from a casein and a whey protein hydrolysate formula (71.7%±6.3%) was not statistically significant.

It is known that the calcium content of the diet can affect both active and passive calcium absorption.[19] Compensation for higher calcium intake by down regulation of calcium-binding proteins in mucosal cells of the proximal small intestine is not likely to occur with single doses used in this study. In addition, an effect on passive calcium absorption could only be observed with large differences in calcium intake; the calcium contents of the diets we tested were between 400 mg/L (formula D) and 680 mg/L (formula E). Therefore, it was not surprising that the lower calcium content in formula D (low protein/low calcium) could not be compensated for by a higher relative absorption. Calcium absorption/retention from formula D was lower than from all other formulas; the difference was significant except for formula G. This suggests that when protein levels of formulas are lowered, as was recently proposed,[20] the calcium level should not be lowered.

Calcium retention was also affected by the type of peptides present in the formulas. Thus, retention was lower from hydrolysate formulas based on soy protein and collagen (formulas F and G) than from milk protein–based formulas, with the exception of formula D, which was a casein/whey hydrolysate, but had a lower calcium level combined with a lower protein content. Soy/collagen hydrolysate formulas are presently marketed in Europe; our data suggest that a modest increase in the calcium level may be prudent.

In this study, calcium retention was higher compared with our earlier data determined in older, weanling infant monkeys.[11] As we observed in previous experiments, calcium retention decreases with age, being significantly lower in weanling rhesus monkeys than in suckling animals (S.R., B.L., unpublished data, 1990); this observation was independent of the formulas fed the monkeys. This finding is in agreement with a study by Lachenmaier-Currle and Harmeyer[21] showing that calcium absorption in 7- to 10-week-old piglets decreased twofold when the animals were weaned after 4 weeks compared with their unweaned litter mates.

Zinc retention from formulas was investigated simultaneously in this study. As has been shown for calcium,[11,22] the distribution of the added radiolabel ^{65}Zn among components in infant formulas is similar to the zinc already present (native zinc).[23] In addition, it has been shown that extrinsic labeling gives identical results to intrinsic labeling for both calcium[22] and zinc.[24] This strongly supports the use of an extrinsic label.

Zinc 65 retention was similar from all hydrolysate formulas based on milk proteins, ranging from 17.6%±3.4% to 28.5%±4.2%. Retention of ^{65}Zn from soy/collagen hydrolysate formulas was significantly lower and reached values of 7.4%±3.1% and 10.2%±3.7% of the original dose. These results for zinc retention are well within the range reported from studies in human infants[25] and adults.[26]

For the infant receiving a particular formula, the zinc content of its diet is crucial. Human milk contains about 2 to 3 mg of zinc per liter, but the relative amount absorbed is considered to be higher than from infant formulas.[27] The concentration of zinc in infant formulas varies manyfold, ranging from about 1.9 mg/L in a study by Haschke et al[25] to 4 to 9 mg/L in the hydrolysate formulas used in the present study. By calculating total retention, differences in relative zinc absorption (ie, absorption of the extrinsic radiolabel) were largely eliminated.

Thus, there were no significant differences in zinc retention due to the type of hydrolysate formula given. However, zinc retention was highest from the three formulas containing 2.0 g of protein per deciliter. It has been shown previously that for similar diets protein has a positive effect on zinc absorption.[26] These formulas also had a lower zinc level. This is not likely to affect zinc absorption, since the addition of high levels of zinc to formula does not reduce zinc absorption.[5] As mentioned above for calcium, a lowering of the protein level of infant formula should not be accompanied by a reduced zinc level. In addition, a somewhat higher zinc level in soy/collagen formula might be considered.

Still under discussion is whether inorganic iron inhibits the intestinal uptake of inorganic zinc.[3,10,25,28,29] The formulas from which ^{65}Zn retention was lowest in this study contained about twice as much iron as the other formulas (Table 1). On the other hand, the zinc content in these formulas was higher as well. It has been proposed that the iron-zinc ratio needs to be greater than 2:1 to observe an inhibitory effect of iron on zinc absorption.[9,30] In this study, this ratio was about 2:3. In a previous study, we have shown that a high iron/zinc ratio does not affect zinc absorption in the presence of a meal.[29] Thus, it is not likely that the level of iron had any impact in this study.

Our results indicate that a higher zinc content in milk protein formula (>4 mg/L) does not provide significantly more zinc to the infant. In this context, it should be kept in mind that a high zinc content of formulas potentially could have a negative effect on the absorption and retention of other trace minerals, such as copper.[31] For infant formulas based on soy protein, however, higher concentrations of calcium as well as zinc might be necessary to reach retention values from milk-based products. Various calcium and zinc-binding compounds in milk, such as caseins[1,2] and citrate,[32,33] possibly enhancing absorption and the inhibitory effect of phytate in soy products[3] could explain these observations.

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Male Pseudohermaphroditism Resulting From 17α-Monooxygenase (P-450C$_{17}$) Deficiency in Two Unrelated Guamanians

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• *Objective.*—To report the cases of and to describe two unrelated Guamanian patients with an unusual form of congenital adrenal hyperplasia resulting from 17α-monooxygenase deficiency (P-450C$_{17}$).

***Design.*—Patient series.**

***Setting.*—Referral center.**

***Patients.*—Two phenotypic females of Guamanian descent, unrelated, and referred for evaluation of hypertension and delayed sexual development.**

***Interventions.*—Diagnosis by measurement of specific adrenocortical precursors and initiation of therapy with dexamethasone. Documentation of response by decrease in circulating concentrations of metabolites and decrease in blood pressure.**

***Conclusions.*—The finding of a rare autosomal recessive disorder in two unrelated persons from a small genetic pool in Guam suggests that this may result from the same molecular defect and may be present in this population at an unexpectedly high incidence. Lack of suspicion frequently leads to unnecessary delay in diagnosis of this condition.**

(*AJDC.* 1992;146:592-595)

Deficiency of the 17α-monooxygenase enzyme (P-450C$_{17}$) is a comparatively rare form of congenital adrenal hyperplasia. Its most common clinical presentation as hypertension and absent sexual development is unfamiliar to many physicians accustomed to seeing the virilization and salt loss characteristic of patients with the more frequently occurring 21-monooxygenase deficiency. Since description of the first person with P-450C$_{17}$ deficiency by Biglieri et al[1] in 1966, more than 120 cases have been reported.[2] The metabolic consequences of this block in steroid biosynthesis include deficient cortisol production, corticotropin hypersecretion, excessive secretion of metabolites in the mineralocorticoid pathway, which produces hypokalemia and hyporeninemic hypertension, and the absence of sex steroid production, which results in sexual infantilism in genotypic females or pseudohermaphroditism with a female phenotype in genotypic males.

We have recently studied two unrelated Guamanian phenotypic females with P-450C$_{17}$ deficiency. They have a previously unreported molecular defect that may be unique to and common in this population.

REPORT OF CASES

CASE 1.—This patient presented to an emergency care facility as a 16½-year-old with an earache and tinnitus. She was incidentally found to have hypertension with blood pressure (BP) ranging from 175/121 to 164/108 mm Hg. She was treated with clonidine hydrochloride and scheduled for an outpatient diagnostic evaluation. She failed to keep her appointment, stopped taking the medication, and returned 3 months later when her symptoms recurred. Her BP was 190/130 mm Hg, and she was admitted to the hospital. Review of her medical history revealed no previous symptoms or documentation of hypertension, and she registered no complaints about delayed sexual development or amenorrhea. Her father and older brother were reportedly well and her mother was deceased, the victim of a homicide.

Physical examination showed her to be a well-nourished phenotypic female with a height of 158 cm (50th percentile for 12 years 10 months) and a weight of 50.1 kg (50th percentile for 14 years 2 months). The remainder of the examination was unremarkable except for the absence of secondary sexual development, with Tanner I breasts, no pubic or axillary hair, and no apocrine sweating. Her external genitalia were prepubertal with normal-appearing labia and introitus. A uterus was not palpated by rectal examination. Her initial laboratory data were remarkable for a depressed serum potassium ion level of 2.8 mmol/L with no other electrolyte abnormalities. An electrocardiogram and a cardiac echogram showed left ventricular hypertrophy, while a sonogram of the kidneys and a radionuclide renal flow study were normal. The plasma renin level was suppressed at 0.03 ng·L^{-1}·s^{-1}, and urinary vanillylmandelic acid and hydroxmandelic acid concentrations were normal.

An endocrine consultation was obtained to evaluate her low-renin hypertension and delayed sexual development. Pelvic examination revealed a 4.5-cm blind vaginal vault. No cervix, uterus, or ovaries were detected by physical examination or by pelvic ultrasound. Initial hormonal studies revealed an elevated follicle-stimulating hormone level of over 40 IU/L, luteinizing hormone level of 51 IU/L, and a low estradiol level of less than 0.5 ng/dL. Her peripheral blood karyotype was

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Pretreatment and Postglucocorticoid Suppression Steroid Metabolite Values*

	Normal		Patient 1		Patient 2	
	Mean	Range	Before Therapy	After Therapy	Before Therapy	After Therapy
Cortisol, nmol/L	270	80-580	70	<30	130	. . .
Urinary free cortisol, nmol/d	40	20-70	. . .	. . .	<3	60
Androstenedione, nmol/L	8.3	2.8-17.5	<0.3	. . .	<3.5	. . .
Dehydroepiandrosterone, nmol/L	54.1	10.7-119.6	110.9	. . .	93.6	. . .
Testosterone, nmol/L	17.0	10.4-34.7	<10.4	. . .	<69.3	. . .
Progesterone, nmol/L	9	2-17	218	39	129	22
Pregnenolone, ng/dL	54	20-110	753	44	293	. . .
17-Hydroxyprogesterone, nmol/L	12	1-29	6	2	3	. . .
17-Hydroxypregnenolone, ng/dL	56	15-221	26	<10	<20	. . .
Aldosterone, pmol/L	300	140-2500	40	<30	20	. . .
Deoxycorticosterone, ng/dL	71	2-19	190	5.5	140	35
Corticosterone, ng/dL	460	135-1860	16 000	647	14 523	. . .
18-Hydroxycorticosterone, ng/dL	44	10-72	274	72	271	102

*Normal values are those found in prepubertal children.

46,XY. Steroid hormones were measured in the serum, and a dexamethasone suppression test was performed to establish the diagnosis of P-450C$_{17}$ deficiency and glucocorticoid suppressibility (Table).

Her BP, initially unresponsive to hydralazine hydrochloride treatment, corrected following 5 days of suppression with dexamethasone therapy, and she was discharged from the hospital-receiving 0.5 mg/d of dexamethasone with no requirement for antihypertensive medications.

Two months after initiation of therapy, she was readmitted to the hospital for gonadectomy. Surgical exploration found a gonad measuring 2 × 0.6 cm on the right; this was removed with an "atrophic" left gonad. Histologic examination found no gonadal tissue in the specimen from the left and encapsulated testicular tissue with immature seminiferous tubules, no spermatogenesis, and Leydig's cell hyperplasia in the specimen from the right. No female internal genitalia were identified during laparotomy. Postoperatively, she was given estrogens, and breast development ensued without recurrence of hypertension.

CASE 2.—This patient was referred at the age of 16 years 10 months with diagnoses of hypertension and testicular feminization. She had been discovered to be hypertensive while being evaluated for headaches at age 7 years and was started on antihypertensive therapy with improvement in her symptoms and BP. At age 11 years, she underwent further evaluation of her hypertension with a normal intravenous pyelogram, renal scan, and renal arteriogram. Her urinary vanillylmandelic acid level was normal, aldosterone level was 440 pmol/L (normal, 110 to 830 pmol/L), and plasma renin value was between 0.03 and 0.06 ng·L^{-1}·s^{-1} (normal, 0.25 to 1.25 ng·L^{-1}·s^{-1}). Electrolyte values were normal; the serum potassium level was 3.5 mmol/L, though previous and subsequent values were below 3.0 mmol/L. Her BP was satisfactorily controlled with clonidine and hydrochlorothiazide.

She was next evaluated at age 15 years 1 month for delayed puberty. She had no secondary sexual development and prepubertal serum concentrations of sex steroids, with an estradiol value below 20 pg/mL, testosterone value of 38 nmol/L, dehydroepiandrosterone sulfate level below 69.3 nmol/L, and elevated gonadotropin values with a luteinizing hormone level of 72 IU/L and follicle-stimulating hormone level of 114 IU/L. A pelvic ultrasound study was initially interpreted as showing a small, prepubertal uterus and no ovaries. Her peripheral blood karyotype was 46,XY, and a diagnosis of pure gonadal dysgenesis was made.

When no uterus was detected by subsequent physical examinations, a revised diagnosis of testicular feminization was made and the patient underwent surgical exploration at age 16½ years. No uterus was found, and two 2 × 2 × 1-cm gonads were identified and removed. Histologically, these were normal testes with immature seminiferous tubules. She was given estrogen replacement therapy and continued to take antihypertensive medication. When later referred by her pediatrician for clarification of the diagnoses of hypertension and androgen insensitivity, additional history suggested possible consanguineous parentage, with the father being unknown but questionably a first-generation relative of the mother. Two younger half-sisters and a half-brother are alive, well, and prepubertal.

Physical examination showed her BP to be 106/72 mm Hg (on antihypertensive therapy and sodium restriction), pulse 86 per minute, height 170 cm (90th percentile for age), and weight 76 kg (>90th percentile for age). The examination was otherwise unremarkable except for Tanner V breasts (taking oral estrogen replacement), a well-healed suprapubic surgical scar, and no sexual hair.

Specific steroid studies (Table) confirmed the diagnosis of P-450C$_{17}$ deficiency. The elevated metabolite values were suppressed with glucocorticoid therapy (Table), and she was initially discharged on a regimen of hydrocortisone, which was later changed to dexamethasone; her antihypertensive therapy and salt restriction were discontinued.

COMMENT

These two patients typify the clinical presentation of most subjects with P-450C$_{17}$ deficiency. Both were hypokalemic and hypertensive with suppressed plasma renin values, and neither had evidence of secondary sexual development at ages when such development would be expected. Also, characteristically, the correct diagnoses in both were delayed until adolescence and, in one case, until after several erroneous diagnoses were made. The biochemical findings were distinctive, with elevations of the mineralocorticoid hormones corticosterone, 18-hydroxycorticosterone, and deoxycorticosterone.[3-5] Likewise, the elevated concentrations of progesterone and pregnenolone and ratios of these metabolites to their 17-hydroxylated products were further evidence of the 17-hydroxylation block. With glucocorticoid replacement, the elevated precursor concentrations suppressed, confirming the reversibility.[3,4]

Both of these patients were treated with dexamethasone. Patient 1 was started on a regimen of 0.5 mg, which was gradually decreased to 0.375 mg at bedtime. When she was lost to follow-up after 8 months, her BP was 130/85 mm Hg and her serum corticosterone (115 ng/dL) and deoxycorticosterone (5.6 ng/dL) levels were in normal ranges. Therapy for the second patient was begun at 1.0 mg of dexamethasone and decreased to 0.25 mg each night after 9 months of therapy. Her BP after 1 year of treatment was 139/76 mm Hg, and her corticosterone (111 ng/dL) and deoxycorticosterone (4.0 ng/dL) values were also suppressed to normal ranges. Both patients have had significant weight gain with therapy and have not maintained normal systolic pressures.

Recent reports suggest that this disorder is more varied in its clinical presentation and more complicated in its molecular pathology than previously believed. For example, it is now recognized that the P-450C$_{17}$ enzyme catalyzes 17α-hydroxylation and the 17,20-lyase reaction.[6] In a recent and comprehensive review, Yanase et al[2] have described several clinical variants and correlated some of them with current knowledge of the molecular biology of this gene. Most of the reported cases have shown complete loss of 17α-monooxygenase and 17,20-lyase activity, but 14 cases of isolated 17,20-lyase deficiency were cited.[2]

Clinical differences are notable between and within the variant groups. Hypertension varies from mild to severe, but malignant hypertension is rare,[7] as is normotension.[8,9] Hypokalemia, a common biochemical finding, is usually asymptomatic and has been only occasionally associated with muscle weakness and, in one case, with histologic evidence of hypokalemic myopathy.[10] Differences also occur in sex steroid secretion, with resultant variations in genital and sexual development. Though most patients are phenotypic females, as are the patients described herein, about 10% of the reported cases (19/122) have either normal male genitalia or degrees of ambiguity. It has been suggested that these represent partial 17α-monooxygenase deficiency.[2] There is no correlation of hypertension with genital phenotype, and hypertension or normal BP may occur in nonmasculinized subjects as well as in those with normal male or ambiguous genitalia.

Recommended therapy for affected patients, as with the more common forms of congenital adrenal hyperplasia, is replacement with glucocorticoids, which decrease hypersecretion of corticotropin and mineralocorticoids, especially deoxycorticosterone, and correct the hypokalemia and hypertension. One must also provide sex steroid replacement and consider the need for surgical therapy in some patients. Appropriate therapy usually depresses the abnormally high concentrations of mineralocorticoids, though deoxycorticosterone levels may remain slightly elevated with adequate suppression of other metabolites.[11] Hypokalemia corrects rapidly, but some patients do not correct their hypertension and require additional antihypertensive therapy.[11] Dexamethasone is usually employed in adults in doses ranging from 0.25 to 1.5 mg/d.[11] In growing children, one must balance the increased growth-suppressive effects of longer-acting glucocorticoids[12,13] against less suppressive hydrocortisone, which has greater mineralocorticoid activity.[14] Both of the patients described herein were fully grown, but one was initially treated with hydrocortisone and then her therapy was changed to dexamethasone, while the other's condition was suppressed and maintained with dexamethasone from the time of diagnosis.

In subjects who are to be reared as females, estrogen replacement at the age of puberty is recommended. In some patients whose diagnosis is not established until an older age, there may be some reluctance to begin estrogen therapy.[11] Estrogen adds another theoretical complication in that it has been reported to aggravate hypertension.[15] This has not been reported as a practical problem in this disorder. Growth of genital hair can be stimulated by androgen therapy.[16] Though infertility is the rule in genotypic females, there is one report of a successful pregnancy following the use of gonadotropin-releasing hormone analogs and in vitro fertilization.[17] In genotypic males, the intra-abdominal testes should be removed in view of their predisposition to undergo malignant degeneration; one Sertoli's cell adenoma in a P-450C$_{17}$-deficient subject has been reported.[18]

Perhaps the most important recent advances in our knowledge of this disease have been the definition of several molecular lesions responsible for the enzymatic deficiency. Six specific molecular changes have been described, five of which lead to P-450C$_{17}$ deficiency[2,19-23] and a sixth that produces isolated 17,20-lyase deficiency.[2] All of the lesions so far described are in structural rather than regulatory sequences. The changes constitute a mixture of base substitutions, duplications, or deletions that lead to major changes in the primary or, presumably, secondary structure of the enzyme and loss or significant decrease of activity.[2] With the exception of two persons descended from an inbred religious sect, all of the molecular defects described in this disorder are different.

The appearance of two affected and unrelated persons from a small gene pool in Guam raised the possibility that these subjects represented a new genetic defect. There was a possibility that the gene had been imported with Japanese migration, since 17α-monooxygenase deficiency is a common disorder in Japan, with at least 35 cases reported.[24] But there was also a prospect that they represented a new mutation common to the native Chamorro population. It has now been shown that these two subjects share the same molecular lesion, not previously described, which involves a single base change of CCC to TCC in exon 1,[25] resulting in an amino acid change of serine to proline.

CONCLUSION

We have found two unrelated Guamanian patients with P-450C$_{17}$ deficiency resulting from a previously undescribed, single-base change in the structural gene. These subjects manifested the classic phenotype described in this condition, with hyporeninemic hypertension, hypokalemia, and, in these cases, male pseudohermaphroditism. Given the occurrence of the same genetic lesion in these two patients and our small sample of this population, it is possible that this condition exists with unsuspected frequency in Guam.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Ethics Case Review in Health Care Institutions: Committees, Consultants, or Teams?

Michael D. Swenson, MD, PhD, Ronald B. Miller, MD
(*Arch Intern Med.* 1992;152:694-696)

Improvement in 'Stat' Laboratory Turnaround Time: A Model Continuous Quality Improvement Project

Edward I. Bluth, MD; Douglas J. Lambert, MBA;
Thomas P. Lohmann, MD; David N. Franklin; Meg Bourgeois, RN;
Carl G. Kardinal, MD; Joseph R. Dalovisio, MD;
Melva M. Williams, MT(ASCP); Arlene S. Becker, RN
(*Arch Intern Med.* 1992;152;837-840)

The Pediatrician's Documentation of Child Maltreatment

Howard Dubowitz, MD, Donald C. Bross, JD, PhD

• Pediatricians are increasingly involved in the assessment of suspected child maltreatment. These assessments are a crucial component of the overall evaluation of the patient and provide the basis for interventions to protect the child. An accurate documentation of the pediatrician's assessment is important to convey the information to professionals in the public agencies involved, including the legal system. However, there may be uncertainty among pediatricians concerning what should be documented in the medical record in cases of child maltreatment. The objectives of this article are to provide a detailed but generic description of the information that should be gathered during the evaluation of children who show signs of any form of child abuse and neglect and to provide clear guidelines for the proper written documentation of child maltreatment.

(*AJDC.* 1992;146:596-599)

The pediatrician's responsibility to identify and report suspected child maltreatment has been well established.[1] Standard pediatric texts include sections on child abuse and neglect, and pediatric journals regularly publish articles in this area. In addition, numerous books and monographs have been published on the medical aspects of child maltreatment. However, the specific components of the pediatrician's assessment, particularly the chart documentation, have not been fully clarified.

Assessment and documentation are especially important in cases of child maltreatment with regard to the possible involvement of the legal and judicial systems. The physician's assessment is a key component of the overall evaluation and it lends substantial weight to the adjudication and intervention by public agencies that are mandated to protect children.[2] For example, a state's attorney's decision to prosecute an alleged perpetrator or to seek a protective order for a child might primarily be determined by the medical assessment. It is important that the pediatrician conduct a thoughtful and thorough assessment that includes proper written documentation of the assessment in the medical record.

Good chart documentation is important for several reasons. The medical record serves as a legal document and is a valuable source of information to the public agencies, ie, child protection services, police, and judicial systems that are involved in these cases. The accuracy and completeness of this documentation facilitates the work of professionals in these agencies. There is often a delay of months to years before a case is heard in court. Complete documentation of the assessment serves to refresh the pediatrician's memory about details of the case that might be long forgotten. Even though the majority of child maltreatment cases do not involve the judicial system, it is prudent to always consider the possibility of legal involvement. Data on the evaluation that are not included in the record might not be admissible as evidence in court based on the judicial view that evidence that is not documented might not be trustworthy. Clear and comprehensive documentation might obviate the need for the pediatrician to testify, particularly in civil proceedings or juvenile court. Criminal trials, however, almost always require a physician's testimony in court.

The pediatric approach to the assessment of child maltreatment is variable. Examples of this approach are the use of colposcopy in sexually abused children, the determination of at what threshold hitting a child is considered abusive, and guidelines for reporting instances of neglect to child protective services. One objective of this article is to provide a detailed but generic description of the kind of information that should be gathered in the evaluation of children who are suspected of having been abused or neglected. The great diversity of issues arising in different abuse and neglect situations, however, is beyond the scope of this communication.

The second objective is to provide clear guidelines to help physicians properly document their assessment of child maltreatment. The incompleteness of medical records of cases of child maltreatment has been demon-

Edited by Peggy C. Ferry, MD

Editorial Comment.—*At first glance, it might seem that some of the points made in this article would go without saying. It is easy to overlook important details in our busy, harried lives as practitioners. Nonetheless, child protective and legal authorities need accurate, well-documented medical information in order to carry out their tasks effectively. So read on, and document, document, document.—P.C.F.*

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strated.[3] There is frequent uncertainty, and perhaps anxiety, about what to write in the medical record. For example, it is not unusual for residents to record the diagnosis as, "Rule out sexual abuse," rather than record a more definitive interpretation of the findings or a brief formulation of what appears possible or probable.

GENERAL ISSUES

Legal Document

The medical record is a legal document that can be subpoenaed by any or all of the participants in a court proceeding. Documentation in the record should therefore be as clear and comprehensive as possible. It should be chronological and businesslike with any corrections inserted as chronological addenda.

Choice of Words

The words and phrasings recorded should be carefully considered. Important statements by the child or parents should be quoted verbatim. Discrepancies between the history and the injury can be very useful in assessing the likelihood of abuse. Statements can constitute valuable evidence and might be admissible in court even though it is considered to be hearsay. *Hearsay* is an out-of-court statement made by another person that a physician may be allowed to repeat in court. It is up to the lawyer offering the physician's testimony to establish to the judge's satisfaction that necessary conditions have been met, permitting the hearsay to be presented in court. While a pediatrician might feel uncomfortable describing the lurid details of a case or reporting foul language, specific documentation will assist the assessment and adjudication of a case.

Medical records are often used by professionals in other disciplines in cases of maltreatment. When maltreatment is suspected, the pediatrician can facilitate the use of these records by other professionals by avoiding jargon and abbreviations such as R/O, WNL, SNAT, SDH). Medical terms can often be replaced by "plain" English, eg, use red instead of erythematous, or terms can be explained in parentheses, eg, subdural hematoma (a collection of blood inside the skull, around the brain).

Descriptions of parents should be professional and never pejorative. Words such as "stupid," "dirty," and "smelly" should be omitted. The possibility that parents may obtain access to the record should be kept in mind.

Legibility

Illegible handwriting is a frequent obstacle to the use of the record. If need be, print, type, or dictate. The signature and title of the medical student, resident, or attending physician should be legible and the signature should also be accompanied by the printed name.

Subjective Opinions

Based on the available data, subjective but professional opinions are appropriate. As always, it is important to justify the opinion. For example, if a father appeared inebriated during a visit, the smell of alcohol on his breath or his slurred speech should be noted. In general, information such as a severe fracture in an infant that is without any plausible explanation "speaks for itself" and has the greatest impact in the legal system.

In some cases, the pediatrician might be reluctant to render an opinion if he or she does not feel certain of its accuracy. For example, the father's possible inebriation might be completely excluded from the record. However, it is preferable to include a careful description of all pertinent data with a tentative diagnosis or interpretation of the findings. Pediatricians need not allow themselves to be pressured into rendering an opinion that they are not comfortable with. At times, professionals from other agencies are eager to obtain a definitive medical diagnosis even though the data are ambiguous or the pediatrician is unsure of the diagnosis. There can be far-reaching ramifications of the pediatrician's opinion, such as appropriate or inappropriate placement of a child in foster care, so clearly the medical assessment should be as accurate and reasonable as possible. Conversely, pediatricians should be firm and convincing in situations where there is strong evidence of maltreatment. A physician is permitted to state that an opinion is based on a "reasonable degree of medical certainty."

SPECIFIC ISSUES

Background Information

The following items should be recorded by the physician: the date and time of the assessment because physical findings can change rapidly, the names of the accompanying adults and their relationships to the child, the referral source, and the "reason for referral" or "chief complaint."

History of the Alleged Maltreatment

Useful approaches to interviewing children about alleged maltreatment have been described elsewhere.[4,5] Generally, a child and parent should be interviewed separately, and the notation in the medical record should clearly identify what information was provided by which person. It is helpful to document the question or context that led to a particular answer or comment to interpret the response. For example, it is quite different if a 4-year-old nods her head when asked, "Did daddy hurt you there?" contrasted with her saying "daddy" when asked, "Who hurt you there?" It is important to use open-ended questions, eg, "Can you tell me what happened?" and to avoid leading questions such as, "Did daddy hurt you there?"

The demeanor and affect of persons providing the history should be documented because this helps to assess the credibility of the history as well as their responses to the maltreatment. For example, was the child in obvious pain or highly agitated and frightened? Was the parent worried about the child or angry about having to answer questions regarding the child's care at the time of the injury?

The notation should include the following information, as appropriate.

1. Who: (*a*) witnessed the incident(s), (*b*) discovered the injury, (*c*) revealed the maltreatment (to whom did they reveal it), (*d*) provides care for the child, (*e*) are the child's babysitters, (*f*) lives in the home, and (*g*) is the alleged or possible perpetrator(s)?
2. Where did the incident(s) occur and were other family members or caretakers present?
3. What: (*a*) was the child doing at the time of the incident, (*b*) do others describe as having happened, (*c*) did the child describe as having happened, (*d*) symptoms and signs have been noted, (*e*) treatment or intervention has been implemented?
4. When: (*a*) did the incident occur (be as specific as possible), (*b*) was health care sought (from where was it sought), and (*c*) was a report made to the Department of Social Services or the police (and by whom)?

History

The history is often key to interpreting the current situation, particularly in neglectful situations and Munchausen syndrome by proxy, where the pattern of incidents is crucial. This history might be obtained from the family, by a review of the medical record, the medical "passport" for foster children in some states, and from the social worker involved in the case. It is particularly important to confer with the child's primary health care provider after a release of and/or a request for information has been obtained.

Relevant history includes prior concerns about abuse or neglect, previous involvement of child protective services or the police, a suspicious pattern of injuries, ingestions, or illnesses, and noncompliance with child health supervision and other health care recommendations.

Psychosocial History

The medical findings alone often do not allow definitive conclusions to be drawn about the likelihood of maltreatment. The optimal assessment of these cases requires a comprehensive understanding of the child's situation within his or her family and this requires the integration of the above information with a psychosocial evaluation of the family. Depending on the setting, it is possible that most of this evaluation will be conducted by a social worker.

The following are important areas to cover in the psychosocial history are: first, the details of the family and household situation, the primary caretakers, the marital status, the employment status, the sleeping arrangements of the members of the family and household, and who feeds the child and who is responsible for toilet training and discipline.

Second, is there a history of maltreatment in the family? For example, have any siblings been reported to child protective services? Is there a history of violence between the spouses?

Third, are there stressors on the family, such as a housing problem, inadequate funds for food, problems in coping with a child's difficult behavior, the recent loss of a job, a divorce, or a death in the family?

Fourth, are there any alcohol or substance abuse problems in the family?

Fifth, what are the parents' coping strategies, supports, or current interventions? Are they involved in community groups?

And sixth, what is the caregiver's view of the child? Does the caregiver think that the child is easy or difficult to care for?

Physical Examination

A complete examination should be performed. This helps to allay the child's anxiety by repeating a familiar routine, and occult signs of trauma, eg, retinal hemorrhages or a suspicious, healed burn scar, might be found.

All abnormal (and relevant normal) findings should be carefully documented. Even if the interpretation of the finding is uncertain, a detailed description is valuable. This requires appropriate knowledge of anatomy, particularly of the female genitalia, in cases of sexual abuse. The deficits in physician knowledge in this area have been demonstrated[6] and need to be addressed in residency programs and during continuing medical education offerings.

Color photographs can provide excellent documentation of the physical findings.[7] If one does obtain photographs, careful attention should be given to include a measurement scale, the date, and the child's name. Color scales can be helpful but are not essential. Slides and photographs are most useful to demonstrate the general characteristics of the injury because the dating of bruises often requires seeing the actual injury. In some jurisdictions, the crime laboratory of the police department might photograph the child. Photographs of good quality can be especially compelling as evidence in court and provide a vivid picture of the findings. Bite marks can be better portrayed for forensic odontologic study by using high-quality black and white (rather than color) photographs.

Although advisable when possible, there is generally no law that requires physicians to take photographs of children they suspect of having been maltreated. A well-labeled sketch or diagram can be adequate. However, both photographs and sketches should be accompanied by a detailed description, for example, "A purple, tender bruise, 9×4 cm, appears horizontally across the left buttock. The well-defined rectangular border suggests this resulted from being hit with an object such as a belt or a piece of wood." Without photographs or a clear diagram, a judge or jury may not be able to fully appreciate the extent and severity of the injuries.

Growth, Development, and Behavior

Growth measurements, including head circumference in infants under 18 months of age, should be plotted. Growth records are important to document possible growth deficiency (failure to thrive) that might reflect child neglect or other psychosocial problems. Tanner staging of breast development, pubic hair, or male genitalia should be included in the assessment of children alleged to have been sexually abused.

A screening evaluation of the child's development and behavior frequently provides valuable information. For example, knowledge of the child's gross motor abilities can help assess whether a history of "climbing out of the crib" is plausible. A history of declining school performance and grade retention or sexual acting out behavior might heighten concern regarding the likelihood of abuse. In addition to contributing to the assessment of possible maltreatment, an evaluation of a child's development and behavior could prompt appropriate interventions regardless of the cause.

Parent-Child Interaction

The relationships and interactions among family members have direct bearing on the assessment of possible maltreatment, on the assessment of the risk to the child if he or she remains in the home, and on the planning of appropriate interventions. For example, there is an immense difference between a parent who is concerned, knowledgeable, and supportive of a child compared with a parent who appears indifferent, uninformed, or hostile to a child. These interactions among family members should be sensitively observed and documented.

Special Investigations

Various protocols have been proposed to evaluate different forms of maltreatment that occur under varying circumstances.[8,9] Physicians should be familiar with the recommendations and procedures of their institution or region and should conform to those guidelines. As mentioned earlier, clear standards of practice have not yet been developed for most conditions, and there is still considerable flexibility regarding what is considered "reasonable practice."

Most jurisdictions have established protocols to evaluate alleged victims of rape. These protocols should be used if it is possible that the child was sexually abused or assaulted within the last 72 hours. All special investigations and laboratory tests should be documented and the results described as "pending" if not yet available.

Diagnosis and Formulation

There is a tradition in medicine of making a diagnosis using only one word or brief phrase. Most cases of maltreatment are not amenable to such brevity, and a few sentences that interpret the findings and describe the formulation of the case are especially useful.

The diagnosis or formulation should be as definitive as possible. If the physician is unsure of what the findings indicate, the use of terms such as "possible" or "probable" is reasonable. For example, instead of a "diagnosis" of "rule out sexual abuse," the following is suggested terminology to use in the written record: (1) the results of the examination were normal, but this does not rule out the possibility of sexual abuse; (2) the results of the examination were equivocal, but it is uncertain whether this is normal or abnormal; (3) the results of examination were abnormal, this is consistent with a history of sexual abuse; (4) the results of the examination were abnormal, this is indicative of sexual abuse; or (5) the results of the examination were abnormal, but this is unrelated to sexual abuse.

The medical assessment should be integrated with the psychosocial data to reach a comprehensive evaluation of the situation. This evaluation should address the likelihood of maltreatment. A summary statement might be, "It appears highly probable that (insert name of child) was sexually abused in the way he or she has consistently described," or "It is clear that (insert name of child) was neglected in that his or her parents repeatedly did not give him or her the asthma medications as prescribed," or "It is most likely that the subdural hematoma (blood around the brain) and retinal hemorrhages (bleeding in the eye) that were seen in this infant occurred as a direct result of a shaking injury and are a form of child abuse."

Plan and Disposition

The details of the plan and disposition should be thoroughly documented. This includes any treatment given and the follow-up recommended. Attention to specific health care needs as well as to the prognosis is useful when planning for children who are placed out of the home and for whom a particular level of care must be found. In addition, any consultations obtained and reports made to public agencies such as the police or child protective services should be documented.

COMMENT

The assessment and documentation of possible child maltreatment requires considerable time and effort. However, the important role of the pediatrician in the area of child abuse and neglect can be facilitated by a clear understanding of what is necessary and, when needed, useful to the legal system. Adherence to these general principles can protect children and aid families by enabling pediatricians to work more effectively with the legal and social service systems. If the physician is required to testify in court, a review of other articles or books will help the pediatrician to know his or her rights as a witness and to know how to work with lawyers.[10,11]

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

The Landau-Kleffner Syndrome or 'Acquired Aphasia With Convulsive Disorder': Long-term Follow-up of Six Children and a Review of the Recent Literature

Philippe F. Paquier, MA; Hugo R. Van Dongen, PhD;
M. Christa B. Loonen, MD (*Arch Neurol.* 1992;49:354-359)

Lacerations Involving Glass

The Role of Routine Roentgenograms

Jeffrey R. Avner, MD, M. Douglas Baker, MD

• *Objective.*—To determine, when evaluating a laceration caused by glass, whether seeing that the bottom of the wound is free of glass eliminates the possibility that glass is present in the wound.

***Research Design.*—Prospective patient series.**

***Setting.*—Two pediatric emergency departments.**

***Participants.*—226 children with lacerations due to glass occurring in a period of 21 months.**

***Selection Procedures.*—Consecutive sample.**

***Interventions.*—Before obtaining a roentgenogram, the triage nurse or the managing physician visually inspected each wound and recorded whether the bottom of the wound was seen, if glass was seen in the wound, and the length and depth of the wound. Further treatment of the wound was at the discretion of the managing physician.**

***Measurements/Main Results.*—Glass was seen in the wounds of 10 children on initial inspection. Of the remaining 216 injuries, glass was contained in 12 (21.4%) of the 56 lacerations when the bottom of the wound was not visualized, and in 11 (6.9%) of the 160 lacerations when the bottom of the wound was visualized. There was a significant association between the depth of the wound and an inability to see the bottom of the wound, and deeper wounds were significantly more likely to contain glass. All but one of the lacerations containing glass had a depth of at least 0.5 cm.**

***Conclusions.*—In the population studied, seeing that the bottom of the laceration was free of glass reduced, but did not eliminate, the possibility that glass was present in the wound. In addition, superficial lacerations (<0.5 cm) rarely contained undetected glass fragments. We recommend that further investigation concerning the mechanism of injury, the depth of the wound, and the type of glass involved is needed before physicians abandon routine roentgenography for lacerations due to glass.**

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Accidents involving glass are a common cause of injury in childhood and are responsible for approximately 20% of all lacerations seen in urban pediatric emergency departments.[1] Essential to the treatment of these injuries is the assurance that no glass remains in the wound before closure. Fragments of glass in a wound may lead to persistent pain, delayed healing, increased scarring, neuropraxis, and an increased risk of infection.[2-5] Since most glass is radiopaque,[6-8] roentgenograms are often obtained in the evaluation of such injuries to identify retained fragments of glass. Some texts[3,9,10] support routine roentgenographic examination as part of the evaluation of all lacerations due to glass. However, one treatment strategy to avoid roentgenography is to assume that seeing the bottom of the wound is free of glass means there is no glass fragment embedded in the wound. Our study was designed to answer the following question: Does seeing that the bottom of the wound is free of glass eliminate the possibility that glass is present in the wound?

PATIENTS, MATERIALS, AND METHODS

This study was conducted in two pediatric emergency departments, The Children's Hospital of Philadelphia (Pa) and The Bronx Municipal Hospital Center (NY), for a period of 21 months. All children who presented during the study period for evaluation of a laceration due to glass were enrolled prospectively. Before obtaining a roentgenograph, the triage nurse or the managing physician visually inspected each wound and recorded whether the bottom of the wound was seen, if glass was seen, and the length and depth of the wound. Posteroanterior and lateral roentgenograms of the injured area were obtained using standard foreign body technique (Kodak RA film, Kodak, Rochester, NY, or Cronex film, Dupont, Wilmington, Del, Lanex regular screen, 46 to 50 kV and 1.6 mAs). The results were reviewed with an attending radiologist who was aware of the etiology of the laceration. Further treatment of the wound was at the discretion of the managing physician. Demographic data, type of glass involved, body part injured, and complications of the injury were collected on evaluation in the emergency department. Roentgenography was then performed and the results were reviewed. Data organization and analysis were done with the Epi Info System developed by the Centers for Disease Control.[11] Analysis of variance was used to compare continuous data and χ^2 was used to compare categorical data.

RESULTS

During the 21-month study period, there were 231 lacerations due to glass. This represented 0.2% of all pediatric emergency department visits during that period. Five cases in which the data sheet or roentgenograms

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Table 1.—Type of Glass Involved in the Injury

Type of Glass	No. (%)
Bottle	83 (36.7)
Window	42 (18.6)
Drinking glass	26 (11.5)
Mirror	9 (4.0)
Vase	6 (2.7)
Table	6 (2.7)
Dish	6 (2.7)
Other	16 (7.1)
Unknown	32 (14.2)

were not obtained at the time of the initial visit were eliminated from the study. Of the 226 children enrolled, 69% (n = 156) were boys. The mean age was 7.3 years. More than eight sources of glass were identified as causative agents (Table 1).

The injuries involved the arms or hands in 119 children, the legs or feet in 79 children, the face or scalp in 25 children, and the torso in three children. Five of the children with lacerations had complications; one needed operative removal of a retained glass fragment, one needed a skin graft, and three had tendon lacerations. Glass was present in 33 (14.6%) of the wounds; 17 (52%) involved the upper extremity, 15 (45%) involved the lower extremity, and one (3%) involved the scalp. In two injuries, small fragments of glass were left in the wound.

Of the 226 patients enrolled, 10 were excluded from further analysis because of obvious contamination of the wound with glass. Of the remaining 216 patients, the bottom of the wound was visualized on initial examination in 160 patients, whereas the bottom of the wound was not visualized in 56 patients. Of the 160 wounds in which the bottom was visualized and thought to be free of glass, 11 were found to contain glass on routine roentgenograms.

The relationship between visualizing the bottom of the wound and finding glass in the wound on roentgenograms is shown in Table 2. Glass was contained in 12 (21.4%) of the 56 lacerations when the bottom of the wound was not visualized, and in 11 (6.9%) of the 160 lacerations when the bottom of the wound was visualized. Thus, the sensitivity of 52% (ie, not visualizing the bottom of the wound to predict a retained glass fragment) was relatively low (95% confidence interval, 31% to 73%). The depth of the wound correlated with finding glass buried in the wound. There was a significant association between the inability to visualize the bottom of the wound and the depth of the wound (0.52 cm vs 0.85 cm, $P<.0001$). Furthermore, wounds that contained glass tended to be deeper (0.76 cm vs 0.56 cm, $P<.05$). All but one of the lacerations containing glass had a depth of at least 0.5 cm (range, 0.2 to 2.5 cm). An approach that uses routine roentgenography for lacerations of at least 0.5 cm had a sensitivity of 96% (95% confidence interval, 78% to 99%), identifying 22 of the 23 wounds with retained glass not detected on initial inspection. Neither the type of glass nor the length of the laceration was associated with detecting glass in the wound.

COMMENT

Part of the difficulty in treating wounds that are caused by glass is the detection of retained fragments of glass. Frequently, patients do not know whether the glass has simply cut them or has remained embedded in the tissues.[10] Furthermore, the initial examination, including palpation of the wound, often gives no indication. Anderson et al[4] reported that physicians who initially treated a series of hand injuries missed the diagnosis of a retained foreign body in 75 of 200 consecutive cases. With the realization that most glass in use today is radiopaque,[6-8] routine roentgenography is often recommended in the evaluation of such injuries.[3,9,10] Still, many physicians do not routinely obtain roentgenograms.[4,12] One risk management strategy to avoid obtaining a roentgenogram of every laceration involving glass is to assume that if the bottom of the wound is visualized and there is no glass seen in the wound, then there is a very low likelihood of any glass fragment embedded in the wound.

Table 2.—Relationship Between Visualizing the Bottom of the Wound and Finding Glass in the Wound on Roentgenography*

Bottom Visualized	Glass on Roentgenogram: Yes	No	Total
No	12	44	**56**
Yes	11	149	**160**
Total	**23**	**193**	**216**

*Sensitivity = 52% (95% confidence interval, 31% to 73%), specificity = 77%, positive predictive value = 21%, and negative predictive value = 93%.

We chose to exclude the 10 children who had glass visible on initial examination since the presence of glass should mandate a roentgenogram to ensure that all the glass was removed. In our sample of the injuries in which there was no glass visualized in the wound, 11 (6.9%) of the 160 wounds of which the bottom was visualized contained glass on roentgenographic examination. Thus, the negative predictive value of 93% (ie, seeing that the bottom of the wound is free of glass in predicting the absence of retained glass) was high. However, if the goal is to detect every case of retained glass, we would strive for a test sensitivity of 100%. In our study, glass was contained in only 12 of the 23 wounds of which the bottom was not visualized, yielding a relatively low sensitivity of 52% (95% confidence interval, 31% to 73%). Thus, if we had adopted the policy of not obtaining a roentgenogram for lacerations in which the bottom of the wound was seen to be free of glass, 149 unnecessary roentgenograms would have been avoided, but 11 lacerations would have been closed with retained glass fragments. It is unknown how many of these wounds with unrecognized retained glass fragments would have developed associated complications if the wound was closed. However, inasmuch as the possibility of persistent pain, infection, and delayed healing could have been prevented, attempts to detect retained glass fragments at the initial visit appear warranted. In fact, the failure to diagnose a foreign body in a wound is a common cause of successful closed-claim malpractice actions against emergency department physicians.[13]

We also studied whether the depth of the wound was a contributor to finding glass buried in the wound. As one would expect, wounds in which the bottom was not visualized were deeper, as were wounds that contained glass. This supports the view that more superficial injuries may not need to undergo routine roentgenography since the possibility of missing a glass fragment is low. In the study population, if all wounds less than 0.5 cm were inspected for glass and all wounds of at least 0.5 cm received roentgenographic examination, only one case of retained glass would have been missed. The sensitivity of this selective approach was 96% (95% confidence interval, 78% to 99%). However, one should realize that even in the population studied, this was not 100% effective in eliminating the need to perform roentgenography.

We chose to have the managing physician or the triage nurse visually inspect the wound and note if the bottom could be seen. Although this is only a preliminary examination, it is often used in busy emergency departments to decide if a roentgenogram of the involved area should be obtained. In addition, we were unable to measure what degree of confidence the examiner had that the bottom of the wound was visualized. While it is possible that a more extensive initial examination, which would include a thorough probing of the wound, by a more experienced physician may have identified some of the cases of retained glass fragments, we believe our data more accurately reflect the decision-making process in busy emergency departments.

Routine roentgenography is the modality of choice for the initial investigation of glass foreign bodies due to wide availability, ease of use, and low cost.[14] Ultrasound examination has been shown to be extremely sensitive in detecting the presence of both opaque and nonopaque foreign bodies in soft tissue, and in detecting the precise location on the foreign body beneath the skin surface.[14,15] Although currently not routinely used for this purpose in either study institution, as this technique becomes more readily available, it may serve as an important adjunct for evaluation of these injuries.

Our study also did not investigate whether the mechanism of the injury correlated with the presence of retained glass. One might suspect that a laceration sustained during a fall onto the glass of a shattered bottle may have a higher incidence of retained glass than a laceration from scraping an arm along a broken windowpane. The addition of this information to our database may eventually allow more judicious use of roentgenography for these injuries.

CONCLUSIONS

We conclude that in the population studied, seeing that the bottom of the laceration was free of glass reduced, but did not eliminate, the possibility that glass was present in the wound. In addition, superficial lacerations (<0.5 cm) rarely contained undetected glass fragments. We recommend that further investigation concerning the mechanism of injury, the depth of the wound, and the type of glass involved is needed before we abandon routine roentgenography for lacerations due to glass.

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The Physical Health of Children in Kinship Care

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• *Objective.*—**The objectives of this study were to assess the current and chronic health problems and the adequacy of primary health care of children placed with a relative (kinship care) by a public agency.**

Research Design.—**Population survey.**

Setting.—**Children in kinship care in Baltimore, Md.**

Participants.—**Four hundred seven (78%) of 524 children in kinship care in 1989.**

Interventions.—**None.**

Measurements/Main Results.—**Information on the child's health status and care was obtained via a review of medical records; questionnaires sent to primary care physicians, parents, care givers, and caseworkers; and clinical assessment of the child by a nurse, pediatrician, and child psychologist. The children were found to have health problems similar to those in foster and poor children, but more problems than American children in general. Frequent diagnoses included impaired visual acuity and hearing, obesity, dental caries, and asthma; often, these problems had not been identified or treated. Gaps in the medical records precluded firm conclusions concerning the children's primary care, but suggest an inadequate system for ensuring their health care.**

Conclusions.—**There is a need for improving the system of health care for children in kinship care. There is also a need for additional research on this high-risk group of children.**

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The number of American children removed from their parents and placed in substitute care has been steadily increasing. Current estimates suggest there are 400 000 foster children; it is projected that by 1995 this number will exceed half a million.[1] This trend is primarily due to the increasing number of substantiated reports of child maltreatment[2] as well as the increasing problems of acquired immunodeficiency syndrome, drug-exposed newborns, and homeless families.[3]

In accordance with federal law requiring placement in the least restrictive setting,[4] many children are being placed by public agencies in the care of relatives, one type of foster care, also called kinship care. Although a common policy nationwide, the health and well-being of children in kinship care has not been previously studied, to our knowledge.

It is important that kinship care be studied for several reasons. A substantial and increasing number of children are living in kinship care. For example, 46% of foster children were placed with relatives in Illinois in 1990,[5] as were almost half the foster children in New York, NY,[6] and 68% of black foster children in Detroit, Houston, Miami, Seattle, and New York.[7] Major deficiencies have been found in the regular foster care system and these may exist in kinship care as well. Examination of foster children has identified a high prevalence of health problems, including visual and hearing deficits, poor growth, and dental caries[8-14]; often, the problems had not been previously diagnosed or treated. Foster children have also been found to have many developmental and mental health problems, often undiagnosed or untreated.[12,13,15-17] Most important, the lack of an adequate health care system for foster children has been noted.[18,19]

The policy of placing children with relatives has been based on assumptions rather than knowledge.[6] The preference for kinship care is rooted in the notion that "blood is thicker than water," that a relative has a special investment in a member of one's own family, and is thus likely to provide adequate care. A preexisting relationship avoids the trauma of placement with strangers. In addition, the worsening shortage of foster homes has necessitated an increased reliance on kinship care.[1] Finally, the philosophy of "family preservation" has emerged, whereby caseworkers strive to keep the family together.[20] As a result, social service agencies have placed substantial trust in relatives. Screening procedures have been less rigorous than for licensed foster homes, and social and financial support and monitoring have been less than those for foster families.

In contrast, it has been argued that the state must ensure adequate care of children removed from their parents into the state's custody.[21] The quality of the relative's home environment is in question, since these children are placed within the same family (often a grand-

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mother) that raised the parents now deemed unable to care for the child.

The current study resulted from a class action law suit against a city for alleged shortcomings in its foster care system.[21] The city was mandated by a federal court to evaluate and improve its foster care system. This project assessed the physical and mental health and educational status of children placed with relatives. Despite the widespread use of kinship care, this is the first study, to our knowledge, of children in this form of foster care in the United States. This article addresses these five objectives: (1) to assess the children's pediatric primary care, (2) to describe their health problems, (3) to assess whether these problems were being addressed, (4) to compare the health of children in kinship care with the health of foster children and other comparable populations, and (5) to identify risk factors for an increased number of health problems. The mental health and educational data will be reported in separate articles.

SUBJECTS AND METHODS

On April 30, 1989, 524 children were in kinship care under the supervision of the Baltimore (Md) City Department of Social Services. Efforts were made to evaluate the health status of all the children and the extent to which they had received primary care.

Procedures

Data on the health of the children were gathered from three sources: (1) medical records, (2) questionnaires, and (3) clinical assessment.

Medical Records.—Extensive efforts via mailings and telephone calls were made to obtain the medical records from all primary health care providers who cared for the child during placement as well as from the provider immediately before placement. The records were abstracted for primary care (eg, immunizations) and chronic problems (eg, asthma) by trained research assistants.

Questionnaires.—Questionnaires were developed and mailed to biological parents, relative care givers, caseworkers, and current primary health care providers. Follow-up with a second mailing and telephone calls yielded response rates of 33%, 91%, 100%, and 55%, respectively. The questionnaires included information about physical and mental health, demographic characteristics, hospitalizations, use of the health care and child welfare systems, and the kinship family. Adolescents also completed a questionnaire on their health, drug use, and sexual activity.

Clinical Assessments.—A special clinic was established to conduct pediatric and mental health assessments. Care givers accompanied the children on most visits, and teenagers were also interviewed in private. Pediatric assessments included growth measurements, visual acuity screening, hearing and blood pressure testing by a nurse, and a medical history and examination by a pediatrician. No laboratory tests were done as part of this assessment. If follow-up was needed, a referral was made to the child's primary care physician.

All the information was integrated to develop a list of each child's active or chronic health problems. In addition, based on all available information, each diagnosis was rated by the pediatrician as follows: (1) treatment had been received; (2) evaluation or treatment was definitely needed; (3) it was unclear whether a problem had been evaluated or treated or it was unclear whether the suspected problem really existed. To establish interrater reliability, each of the four faculty pediatricians independently rated the information on the same randomly selected 10 children, and these ratings were compared with "correct answers" established by consensus. Division of the number of agreements by the total number of ratings revealed 84% agreement.

Table 1.—Comparison of Children in Kinship Care Examined and Those Not Examined

	Children Examined (n=407)	Children Not Examined (n=117)	P*
Mean age, y	8.1	10.1	.001
Mean age at placement, y	5.4	6.9	.001
Mean duration in care, y	2.7	3.7	.04
Male, %	48	41	NS
Race, %			
Black	91	87	NS
White	9	13	NS
No. of placements, %			
1	61	45	.005
≥2	13	22	NS
Long-term plan, %			
Return to parent	35	35	NS
Adopt/remain with relative	60	55	NS
Unsure	5	11	NS
Care giver a high school graduate, %	42	54	NS
Care giver employed, %	45	33	NS
Care giver's view of child, %			
Easy	47	34	NS
Okay	46	52	NS
Difficult	8	14	NS
Care giver a grandparent, %	58	64	NS
Mean No. of children in home	3.1	2.8	NS

*NS indicates not significant.

Data Analysis

Student's *t* tests, Pearson's correlation coefficients, and one-way analyses of variance were conducted to examine the associations between background variables and number of medical problems as well as number of problems needing evaluation or treatment. Standard multiple regression analyses were done with the significant background variables and measures of health problems.

RESULTS

Sample

Four hundred seven (78%) of 524 children completed a clinical assessment. Comparison of these 407 children with the 117 who were not examined across 12 characteristics yielded four significant differences (Table 1). Compared with those children who were not examined, those examined (1) were younger, (2) were placed in care at a younger age, (3) were in care for a shorter duration, and (4) had lived in fewer homes. The two groups of children were similar with respect to other characteristics, as shown in Table 1.

The assessed children ranged from younger than age 1 year to age 19 years. Most (91%) were black and approximately half were female. The reasons for placement included neglect (75%), physical abuse (20%), abandonment (14%), parental mental health problems (9%), sexual abuse (7%), parent incarcerated (6%), and emotional abuse (2%). More than one reason might have led to a child's removal. Approximately half of the children were placed with a grandmother, a third with an aunt, and the remainder with other relatives.

Table 2.—Primary Care of Children in Kinship Care

	Age Group, y					
	0-5		6-11		12-19	
	No.	%	No.	%	No.	%
Child health supervision	137	...	190	...	77	...
Adequate	...	28	...	26	...	1
Inadequate	...	1	...	10	...	10
Uncertain	...	70	...	64	...	69
Immunizations	137	...	190	...	77	...
Adequate	...	56	...	44	...	38
Inadequate	...	1	...	1	...	4
Uncertain	...	42	...	55	...	58
Blood pressure (age >2 y)	77	...	165	...	76	...
Normal	...	96	...	94	...	86
Elevated	...	4	...	6	...	15
Visual acuity (age >3 y)	55	...	185	...	77	...
Pass	...	47	...	79	...	84
Fail	...	16	...	13	...	10
Untestable	...	37	...	8	...	5
Hearing (age >3 y)	65	...	183	...	73	...
Pass	...	73	...	89	...	92
Fail	...	6	...	9	...	7
Untestable	...	20	...	2	...	1
Adequate dental care (age >3 y)	99	...	189	...	77	...
Yes	...	31	...	43	...	46
No	...	53	...	41	...	43
Do not know	...	17	...	16	...	12

Pediatric Primary Care

Child health supervision was assessed according to the schedule for the Maryland Early Periodic Screening, Diagnosis and Treatment program. Child health supervision was considered "adequate" if the child had received at least two thirds of the recommended visits during the previous 3 years. This lenient threshold was selected because of possibly incomplete records, a common problem for foster children. In about two thirds of the children, it was unclear whether they had met this standard (Table 2). Adequate child health supervision had been clearly received by approximately 25% of children in each age group. Immunization status (Table 2) was assessed according to the Maryland Early Periodic Screening, Diagnosis and Treatment schedule. Again, "adequate" refers to at least two thirds of immunizations required in the previous 3 years. The *Haemophilus influenzae* type b and repeated measles, mumps, and rubella vaccines were excluded since these were recent recommendations. Immunizations were adequate in only 38% (12- to 19-year-olds) to 56% (infants to 5-year-olds) of the children.

Blood pressure was measured once by the nurse in children aged 3 years and older, using the recommended technique. The systolic and diastolic pressures were plotted on the gender-appropriate charts.[22] If either pressure was greater than the 90th percentile, this was labeled as elevated. Clearly, further evaluation is needed to determine whether these children are hypertensive. Fifteen percent of the adolescents had an elevated reading (Table 2). In nearly all the children with an elevated blood pressure, this had not been previously noted.

Visual acuity was screened in children older than age 3 years using the E or Snellen vision charts. For children aged 4 years, visual acuity less than or equal to 20/50 in either eye was a "fail"; for older children, the cutoff was 20/40 (Table 2). A difference of more than one line between the two eyes was also a "fail." Children wearing glasses were tested with them; if they had not brought their glasses, they were "untestable." One of every four children aged 4 and 5 years failed the vision screen test, as did about one in seven of the older children. Among those children diagnosed with a visual problem, approximately half clearly needed further assessment or treatment.

Hearing was screened in children older than age 3 years using pure-tone audiometry. A "fail" was an inability to hear at 30 dB at any of these frequencies: 1000, 2000, or 3000 Hz in a quiet, but not soundproof, room. The possibilities of wax occluding the canal or otitis media were excluded. Similar proportions of children (3% to 9%) in each age group failed the hearing screen test. Few of these children had been previously known to have hearing problems; most required further assessment.

Based on the American Academy of Pediatrics' recommendation that dental visits begin at age 3 years, dental care was assessed for children older than age 3 years by asking the care giver about the child's last dental visit.[23] A visit within the previous year was assessed as "adequate" care. Clearly, this is a minimum standard and adequate care did not preclude the possibility of dental problems. Forty-four percent of children had not received adequate dental care (Table 2).

Table 3.—Common Health Problems and Treatment Status of Children in Kinship Care

	Age Group, y					
	0-5 (n=137)		6-11 (n=190)		12-19 (n=77)	
Problem	%	Treatment Status, %	%	Treatment Status, %	%	Treatment Status, %
Anemia	9	. . .	4	. . .	4	. . .
Treated	. . .	42	. . .	0	. . .	0
Follow-up needed	. . .	8	. . .	14	. . .	0
Follow-up might be needed	. . .	50	. . .	86	. . .	100
Asthma	26	. . .	16	. . .	8	. . .
Treated	. . .	63	. . .	47	. . .	83
Follow-up needed	. . .	11	. . .	20	. . .	17
Follow-up might be needed	. . .	26	. . .	33	. . .	0
Caries	15	. . .	29	. . .	13	. . .
Treated	. . .	14	. . .	14	. . .	10
Follow-up needed	. . .	71	. . .	79	. . .	90
Follow-up might be needed	. . .	14	. . .	7	. . .	0
Other dental	7	. . .	11	. . .	8	. . .
Treated	. . .	20	. . .	29	. . .	33
Follow-up needed	. . .	40	. . .	48	. . .	33
Follow-up might be needed	. . .	40	. . .	24	. . .	33
FTT (weight/height ≤10th percentile)*	9	. . .	6	. . .	1	. . .
Treated	. . .	31	. . .	0	. . .	100
Follow-up needed	. . .	0	. . .	27	. . .	0
Follow-up might be needed	. . .	69	. . .	73	. . .	0
Short stature (height/age ≤5th percentile)	9	. . .	6	. . .	10	. . .
Treated	. . .	8	. . .	17	. . .	38
Follow-up needed	. . .	17	. . .	0	. . .	13
Follow-up might be needed	. . .	75	. . .	83	. . .	50
Obesity (weight/height >95th percentile)	8	. . .	15	. . .	18	. . .
Treated	. . .	0	. . .	4	. . .	0
Follow-up needed	. . .	27	. . .	54	. . .	86
Follow-up might be needed	. . .	73	. . .	43	. . .	14
Orthopedic	4	. . .	3	. . .	13	. . .
Treated	. . .	33	. . .	33	. . .	10
Follow-up needed	. . .	17	. . .	17	. . .	40
Follow-up might be needed	. . .	50	. . .	50	. . .	50
Skin	22	. . .	8	. . .	22	. . .
Treated	. . .	20	. . .	6	. . .	6
Follow-up needed	. . .	23	. . .	19	. . .	65
Follow-up might be needed	. . .	57	. . .	75	. . .	29

*FTT indicates failure to thrive.

Common Health Problems and Treatment Status

The major chronic and current health problems, and their treatment status, are shown in Table 3.

Anemia was frequently reported as a current problem by the care givers, particularly in the newborn to 5-year-old age group. Asthma was common, ranging from 26% of the youngest children to 8% of the teenagers. This assessment was based on both history and examination, and questionable cases of "wheezing" were excluded. Many children appeared to need evaluation of their treatment regimens. Many children had obvious dental caries in need of care. Other dental problems, such as malocclusion, were also quite common.

Growth problems were evident among some children, although, overall, the group did not differ significantly from the norms of the National Center for Health Statistics. Rather, the proportions of children at the extremes of the distribution (ie, wasted, stunted, or obese) were elevated. Based on a weight/height ratio of less than or equal to the 10th percentile, 9% of the children in the newborn to 5-year-old age group were failing to thrive. Short stature was based on a height/age ratio of less than or equal to the fifth percentile; according to this ratio, 10% of the adolescents were short. Obesity, defined as a weight/height ratio greater than the 95th percentile, was relatively common, ranging from 8% of the youngest children to 18% of the teenagers.

As expected, a few problems were common only in specific age groups. Acne was found in almost 15% of the adolescents. Approximately 5% of the children in the two younger groups had atopic dermatitis. Other skin problems, such as seborrhea or diaper dermatitis, were found in 15% of the children in the newborn to 5-year-old age

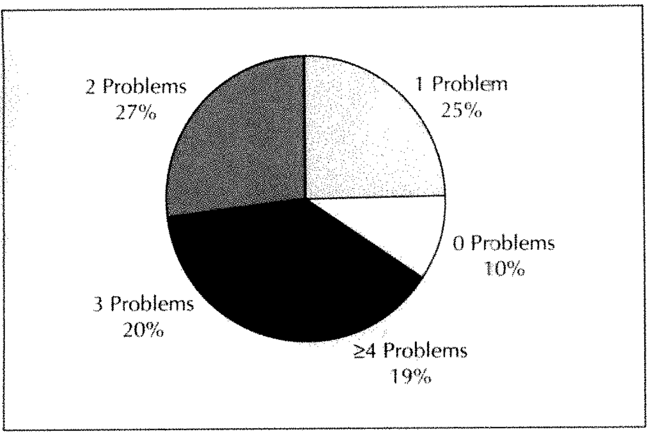

Fig 1.—*Proportion of children by number of medical problems.*

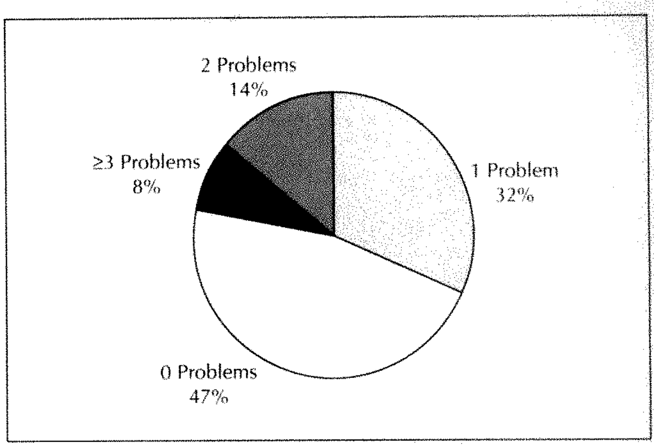

Fig 2.—*Proportion of children by problems needing medical attention.*

group. Thirteen percent of the children younger than 12 years had healed burn scars, mostly reported as resulting from "accidental" contact with a hot iron or curling iron. Orthopedic problems, such as scoliosis, were most common among the teenagers.

A number of problems were surprisingly infrequent. Relatively few children had chronic chest pain, stomach aches, headaches, enuresis, or encopresis. Serious organic disease was also rare. Finally, very few of the teenagers reported problematic health-related behaviors. Only four teenagers admitted to drinking alcohol with some regularity and only one was smoking cigarettes currently. None acknowledged ongoing drug use.

Number of Medical Problems and Treatment Status

The number of medical problems was used as an indicator of health status. The proportion of children by number of problems is presented in Fig 1. Only 10% of the children were free of medical problems. Approximately half had one or two problems and 39% had between three and six problems. The number of problems was similar in the three age groups.

The distribution of children by number of medical problems in definite need of further evaluation or treatment is shown in Fig 2. Based on all available information, many problems had not been addressed.

Risk Factors for Increased Health Problems

Most of the background and demographic variables were *not* significantly associated with increased medical problems or untreated problems. For example, there were no statistically significant associations between number of medical problems and gender, reason for placement, duration in care, relationship or age of care giver, whether the caseworker helped the family obtain health care, or the number of children in the household.

However, several variables were significantly associated with health problems. Children with increased health problems were more likely to have an unemployed care giver ($P = .004$), and their care givers made more frequent contact with the caseworkers ($P = .04$).

Children with increased untreated medical problems were older at placement ($P = .001$) and had evoked a more positive response from other children in the household ($P = .04$). In addition, children who were of school age at the time of the examination had nearly twice as many untreated problems as preschoolers ($P = .0006$). Children with more untreated problems had less-educated care givers ($P = .04$), and the care givers were rated by health care providers as noncompliant with keeping appointments ($P = .02$). Twenty-six percent were rated as "very compliant," 48% as "average," and 26% as "poor." In the multiple regression analyses, background variables accounted for only 4% of the variance in both measures of health.

COMMENT

Children in kinship care have substantial health care needs. Many of their problems had not been previously identified, and when they had been, follow-up often had not been obtained. In some areas, such as immunization status, few conclusions can be reached due to missing data. In view of the extensive efforts made to gather medical information, gaps in health information point to deficiencies in the system that is responsible for ensuring the care of these children. This appears to be a common problem; poor communication among professionals and agencies caring for these children and inadequate documentation have also been found in the foster care system.[6,9] Overall, however, a substantial amount of information was obtained from multiple sources.

We compared our findings with studies of foster children, poor inner-city children, and American children in general (Table 4). The comparison with regular foster children is useful because this is the main alternative for children who are removed from their home. The comparison with poor, inner-city children is informative in that the consequences of maltreatment and placement with a relative might be distinguished from the risks of poverty.[24] Finally, comparisons with the general population can identify the cumulative sequelae of maltreatment, placement with a relative, and poverty. The various studies frequently used different measures and these comparisons should be viewed cautiously.

Child Health Supervision

It is difficult to draw conclusions about the health supervision of the children, given the gaps in the medical records. However, the number of previously undetected problems suggests that adequate primary care had not been obtained for many of the children. Two studies of foster children found that 13%[9] and 48%[8] of children had not had a health supervision visit in the previous year. However, most of those children were of school age, for whom annual checkups have not been recommended. It

Table 4.—Comparison of Health Data in Different Populations

	Children in Kinship Care, %	Foster Children, %	Poor Children, %	American Children, %
Failed vision screen test	29	33[9]	. . .	5-15[29]
	. . .	8-13[14]	. . .	1[28]
	. . .	25-33[10]	. . .	. . .
Failed hearing screen test	7	5.5[9]	3[31]	1[10]
	. . .	3[10]	. . .	1.6[28]
Dental caries	22	3-5[14]	60-90[32]	. . .
	. . .	16[9]	. . .	. . .
	. . .	38[10]	. . .	. . .
Anemia	6	4[10]	2.9[34]	2.7[34]
Asthma	18	4[10]	11[35]	5[28]
Failure to thrive	4	8[10]	1-7[38]	. . .
Short stature	8	12[8]	7-15[38]	. . .
	. . .	12[9]	. . .	. . .
	. . .	25[14]	. . .	. . .

appears that children in this study, and foster children elsewhere, receive less than the recommended preventive pediatric care. Access to health care might be a barrier, although this was not a factor in this study.[25] Given the high-risk status of children in substitute care, at least standard primary health care should be ensured.

Immunizations

Approximately half the children had documentation of most of their immunizations. However, since immunizations are required for school entry, most of the school-aged children were probably immunized. Missing information and inadequate immunizations have been described in studies of foster children,[8,9,18] and national data indicate that approximately 25% of preschoolers and almost 50% of inner-city preschoolers are incompletely immunized.[26,27] Gaps in the health records of children in substitute care are a major problem and preclude firm conclusions about their immunization status.

Elevated Blood Pressure

Although 15% of the adolescents in this study had elevated blood pressure on a single measurement, this represents an excess of 5% of children above the 90th percentile. Many of these children are likely to be normotensive with repeated measurements. Possibly, stress in the lives of these children contributed to the elevated blood pressures, although hypertension has not been identified as a problem in foster children.

Visual Acuity

Eleven percent of children failed the vision screen test. Possible explanations include (1) no recent vision screen testing, (2) no definitive vision examination and visual correction, or (3) a definitive examination did not warrant corrective lenses. Similar or higher rates (up to 38%) of foster children have failed a vision screen test.[9,10,14] A recent national interview survey found a prevalence of only 1% visually impaired children[28]; other national estimates have found refractive errors in 5% to 15% of children.[29,30]

Hearing

More children (7%) failed their hearing screen test than foster children,[9,10] national samples,[10,28] and a low-income population.[31] The reason for this is unclear and repeated examinations are needed.

Dental Care

Dental caries in need of treatment and other dental problems, such as malocclusion, were rather frequent. The lack of routine dental care found in this study has also been found in foster children[9,14] and poor children in general.[32] In 1986, 20% of US children younger than age 5 years and 72% of those aged 5 to 14 years had visited a dentist in the previous year.[33]

Chronic Health Problems

The rate of anemia was similar to that in foster children,[10] but higher than national data.[28] Anemia has been found in fewer than 3% of preschoolers in low-income families or seen in a private clinic.[34]

Asthma was highly prevalent, compared with a national sample of American children (5%)[28] and children in Baltimore (11%).[35] This might be due partly to the increasing prevalence of asthma in urban environments and the higher prevalence of asthma in blacks.[36]

Short stature was a quite frequent finding, although failure to thrive was not. Since weight/height ratios for 10% of the children are expected to be below the 10th percentile, many of these children were possibly normal, but thin. Short stature and growth problems have been described in several studies of foster children.[8-10,13,14,37] A national survey of poor children also found significant growth problems, particularly concerning height.[38]

The rather large number of short children in this study is similar to that found in foster or poor children. Low weight/age or weight/height ratios reflect acute wasting due to mild or short-term undernutrition, whereas short stature suggests stunting, usually due to more severe or long-term undernutrition. In addition to inadequate caloric intake, growth was possibly impaired due to environmental deprivation, such as inadequate parental stimulation or nurturance preceding placement.[39]

Obesity has not previously been identified as a problem in foster children. However, this was a striking finding in our study, with 13% of the children being obese. Obesity is more prevalent among low socioeconomic groups and is also associated with depression,[40] which was a frequent finding in this study.[25]

The finding of infrequent alcohol, cigarette, or drug use among the teenagers probably reflects their reluctance to disclose such behavior to unfamiliar professionals. The low rates contrast sharply with national statistics for adolescents, with alcohol, cigarette, marijuana, and cocaine use in the previous month reported by 31%, 16%, 12%, and 2% of respondents, respectively.[41]

Number of Medical Problems and Treatment Status

The number of types of health problems an individual has serves as a marker of health status and relates to health care utilization.[42] The substantial number of children with health problems is similar to that reported in foster children.[37,13,10] For example, foster children in Baltimore were found to have a mean of 2.3 chronic problems per child, three to five times the national rate.[9] Foster children have been found to generally have more problems than comparable populations in Head Start,[43] in the Job Corps,[44] and in a national sample.[45]

Children in kinship care appear to have similar health problems and health care needs to those of foster children. In several areas (eg, dental problems, visual acuity, and obesity), the prevalence of problems was similar to that of poor children; other disorders (eg, hearing problems and asthma) were more prevalent among the study children. Compared with American children in general, children in kinship care appear to have many more health problems.

There are a few reasons why children in kinship or foster care, mostly from poor families, might have a higher prevalence of certain disorders than other poor children. A child with certain health problems is possibly at increased risk for maltreatment and out-of-home placement.[46] In addition, inadequate health care has been documented in this and other studies of children in substitute care and is a likely contributor to increased medical problems. Some of the conditions might have resulted from earlier abuse or neglect and should not be attributed to kinship care.

There is no clear profile of children with increased health problems or those with untreated problems. This is not surprising given the many factors determining health and the difficulty in identifying these factors. However, a few risk factors were found that offer some guidance in identifying the children with the most health problems. The increased number of health problems associated with unemployed or less educated care givers probably reflects the added vulnerability of poor children to an array of medical conditions or lack of health care.[24] As expected, poor compliance with health care recommendations was associated with an increased number of untreated problems. Care givers were more likely to contact their caseworker if the child had multiple problems, suggesting that caseworkers were seen as a resource.

The increased number of untreated conditions in children placed at an older age might reflect less frequent primary care and a lower level of concern of care givers and caseworkers for younger children. The association between increased untreated problems and a positive response from children in the household could be due to children with health problems being viewed more sympathetically.

An important question concerns the generalizability of the results. This is the first such study of children in kinship care, to our knowledge, and little is known about children living in this arrangement elsewhere. Although there were a few significant differences between the children assessed and those not assessed, these variables were mostly *not* associated with health problems. The many untreated health problems are probably an underestimate, given the association between more problems and older age at placement; the children who were *not* examined were significantly older when placed.

Overall, the findings appear representative of the health problems of children in kinship care in Baltimore and may be typical of children placed with relatives, particularly in poor, urban populations. However, policies and practice concerning out-of-home placement and demographic characteristics of families and children should be compared to assess the generalizability of this study's findings to other areas. There is a need for data on children in kinship care elsewhere.

The findings in this study cannot be interpreted as simply reflecting kinship care. Perhaps many of the problems preceded placement; comprehensive evaluation at the time of placement and follow-up are needed to examine kinship care more closely. A cross-sectional study yielding "censored" data on children in care on a certain date[47] selects children with lengthy stays in care, omitting those soon returned to their parents.

Some questions concerning kinship care require a comparison group, such as foster children, maltreated children who remain at home, or children from low-income families who are not maltreated. It is naturally not possible, however, to randomly assign children to different living arrangements, and significant differences are likely among the above groups. Nevertheless, important clinical needs and systemic deficiencies in the care of these children were identified and need to be addressed independently of the predicament of other vulnerable children. This is the first such evaluation of children in kinship care, to our knowledge, and this type of descriptive study is often the basis for further research.

IMPLICATIONS

Children in kinship care appear to have increased problems, including impaired visual acuity and hearing, poor growth, obesity, dental caries, and asthma. Frequently, the problems had not been addressed. Children in kinship care are in the custody of the state, which is responsible for ensuring and coordinating their care. It is of little comfort that the children in this study did not appear to be significantly worse off than foster or poor children. The number of undiagnosed and untreated problems and the lack of available health information point to serious shortcomings in the child welfare and health care systems.

All those concerned with the health of these children, their relatives, caseworkers, and health care providers must become more sensitive to the needs of these children and help ensure adequate health care for them. Care givers should be informed about the child's health care needs and supported in their efforts to obtain health care. Caseworkers also need training regarding appropriate pediatric care and should ensure that these needs are met. In addition, health care providers should help educate the relatives and caseworkers, while closely monitoring the health of these children.

Most important, there is a need for an improved system to ensure the adequate health care of these children. Useful standards and guidelines have been issued by the Child Welfare League of America[48] and the United Way in Los Angeles.[49] They are appropriate for both foster children and those in kinship care, whose needs appear to be quite similar. Such recommendations for enhancing the health of children in substitute care should be implemented if we are to cease replacing one form of child maltreatment with another.

Finally, there is a need for more research on children in kinship care in other areas. For example, what factors are associated with a successful placement in kinship care? Such information can guide child health and welfare policies and programs for these vulnerable children.

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Equestrian Injuries in Children and Young Adults

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• We reviewed the English language scientific literature about equestrian injuries among children and young adults. All studies showed that more females than males were injured, with falls from horses being the most common cause of injury. Fractures were common, and head injuries were associated with the vast majority of deaths (72% to 78%) and hospitalizations (55% to 100%). Although the overall injury rate was low, equestrian athletes are at risk for serious injuries. Pediatricians should know the medical contraindications for participation in equestrian sports and encourage riders to obtain horse safety training and use protective headgear (helmets) approved by the American Society for Testing Materials when riding or working around horses. Pediatricians can play an active role in increasing public awareness of equestrian injuries and in reducing risk of injury.
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The risk of injury from equestrian activities has been recognized since antiquity. "The grave yawns for the horseman" is an ancient Arab proverb.[1] Some activities, such as jumping during the steeplechase, are inherently risky. Horses can weigh 450 kg (1000 lb) and travel up to 48 km/h (30 mph)[2]; therefore, a person who falls off a horse can sustain severe and sometimes fatal injuries. Children and young adults can also be injured during nonriding activities (eg, being kicked while grooming or leading a horse).[3] According to data from the National Electronic Injury Surveillance System,[4] more than 2300 persons younger than age 25 years are hospitalized annually because of equestrian injuries. The following case history demonstrates the type of injury that can occur:

> A 13-year-old girl was practicing [horse jumping] in preparation for a competition. She fell forward onto the ground. As the horse (which had also fallen nearby) was righting himself, he stepped upon the rider's head. She was found to be unconscious and never demonstrated any recovery of neurological function. Her skull had been fractured at the base, and she died five days following injury. Autopsy revealed extensive bruising and hemorrhage deep within the brain.[2]

Each year, an estimated 30 million Americans ride horses.[5] Although the number of children and young adults involved in equestrian activities is unknown, it is significant. The American Horse Council estimates that in the United States more than 1.2 million horse owners are younger than age 20 years.[6] In 1989, nearly 220 000 4-H youth projects involving horses were reported in the United States; besides 4-H, there are many other equestrian organizations for children and young adults.[7]

We reviewed the scientific literature regarding equestrian injuries among children and young adults to identify the most common types of injuries and their causes. We summarize injury prevention measures and make recommendations for pediatricians with patients involved in equestrian activities.

SUBJECTS AND METHODS

We defined equestrian injuries as those that occurred while riding a horse or that were the result of a horse's behavior (eg, a kick or a bite). We searched English language scientific literature for studies of equestrian injuries or deaths through April 1991. Databases searched (and initial year that periodicals were available for each) included MEDLINE (1966), Sports (1975), Emergency Medicine Base (1974), Commonwealth Agricultural Bureaux Abstracts (1972), National Institute for Occupational Safety and Health Technical Information Center (1973), and the National Technical Information Service (1964). Because we found few articles specifically about children or young adults, we reviewed all studies in which 50% or more of the study population was 25 years old or younger. We excluded studies of jockeys and rodeo participants because their risk factors for injury were likely to be different from those of other equestrians.

RESULTS

Mortality Data

We found only two mortality studies.[1,8] Pounder[1] reviewed coroners' reports of 18 fatalities associated with riding and handling of horses in South Australia from 1973 to 1983. Ingemarson et al[8] analyzed 53 deaths associated with equestrian activities recorded by the Swedish Bureau of Statistics. In both studies, most deaths were among females (80% and 89%) (Table 1). The leading external cause of death was falls; head injuries were associated with more than 70% of deaths.

Hospital Admission Studies

Barber[9] surveyed all cases of hospitalization because of equestrian injuries (154 cases) at the Radcliffe Infirmary in Oxford, England, between 1971 and 1972. McGhee et al[10] reviewed medical records of 59 patients hospitalized with head injuries related to equestrian activities at the Edinburgh Royal Infirmary in southeastern Scotland from 1980 to 1985. Barone and Rodgers[11] reviewed medical charts of 136 patients 19 years old or younger admitted to the University of Virginia Medical Center (Charlottesville) with equestrian-related injuries from 1973 to 1986.

Persons in the three hospital admission studies were also predominantly female (range, 68% to 85%) (Table 2).[9-11] Head injuries occurred in 55% to 100% of persons, with falls being the major external cause of injury. In all three studies, some persons suffered severe injuries. Barber[9] reported that one person died (as a result of head injury), a 2-year-old toddler suffered hemiplegia, and three persons younger than age 13 years developed posttraumatic epilepsy. McGhee et al[10] reported two deaths and three cases of neurologic impairment 1 year after injury. Barone and Rodgers[11] reported no deaths, but noted that one child developed persistent quadriplegia.

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Table 1.—Mortality due to Equestrian Injury Among Children and Young Adults*

	Pounder[1] (N=18)	Ingemarson et al[8] (N=53)
Location	Australia	Sweden
Study years	1973-1983	1969-1982
Subjects aged ≤25 y	10 (56)	27 (51)
Subjects aged ≤25 y who were female	8 (80)	24 (89)
Subjects who were injured as the result of a fall†	15 (83)	28 (53)
Subjects who suffered head injury†	14 (78)	38 (72)

*Except for the first two rows, values are number (%) of subjects.
†Values are for all subjects.

Table 2.—Results of Hospital Admission Studies

	Barber[9] (N=154)	McGhee et al[10] (N=59)	Barone and Rodgers[11] (N=136)
Location	Southeastern Scotland	Southeastern Scotland	Virginia
Study years	1971-1972	1980-1985	1973-1986
% of subjects aged ≤25 y	58	75*	100†
% of subjects aged ≤25 y who were female	68	85‡	76
% of subjects injured as the result of a fall	84§	90	75
Most common injury site (% of subjects)	Head (67)	Head (100)‖	Head (55)
% of subjects sustaining a fracture	Not reported	Not reported	53

*The oldest subject in this subgroup was aged 20 y.
†All subjects were less than 20 years old.
‡Ages were not specified in this study. Value is percentage of subjects of all ages who were female.
§Includes events after falls (eg, trampling and kicks).
‖Study included only subjects admitted to a hospital's head injury unit.

Emergency Department Studies

Williams[12] studied the records of 336 persons with equestrian injuries treated at 18 hospital emergency departments in Colorado, Utah, and Wyoming from 1972 to 1973. Danielsson and Westlin[13] analyzed data from the records of 119 persons listed in an equestrian injury register maintained at the Malmo, Sweden, General Hospital emergency department from 1970 to 1971. Gierup et al[14] studied the records of 174 persons with equestrian injuries treated at hospitals in the Stockholm, Sweden, area from 1972 to 1973. McLatchie[15] reviewed data from records of 115 persons listed in an equestrian injury register at the Dumfries and Galloway Royal Infirmary emergency department in southwestern Scotland from 1977 to 1978. The *MMWR*[4] reported data regarding the estimated number of persons with equestrian injuries treated in hospital emergency departments in the United States between 1987 and 1988; these estimates were based on a sample of hospital emergency departments from the National Electronic Injury Surveillance System.

Like results of the hospital admissions studies, results of the five emergency department studies showed females to suffer more equestrian injuries than males (range, 52% to 87%), with most injuries among all riders occurring in those aged 10 to 19 years (Table 3).[4,12-15] The percentage of persons treated in an emergency department who were subsequently hospitalized ranged from 10% to 38%. Falls accounted for most injuries, with extremities (especially the upper extremities) being the most common site of injury (range, 30% to 61%). Head injury was less common in the emergency department studies than in the hospital admission studies (range, 10% to 28%), but, as in the hospital admission studies, fractures were frequent (range, 28% to 48%).

A different denominator was used in the three studies in which injury rates were calculated: Danielsson and Westlin[13] used number of riding lessons; Gierup et al[14] used number of rides; and McLatchie[15] used riding hours estimated to have occurred in the catchment areas of each of the hospitals (Table 3). Despite the differences, reported rates of injury were consistent, ranging from 0.7 per 1000 rides to two per 1000 riding hours.[14,15] Combined results from these three studies showed that two people died and 29 were impaired for more than 6 months. [13-15]

Equestrian Organization Studies

Each of the studies of members of equestrian organizations reported injuries among different riding populations.[2,5,16] Mahaley and Seaber[2] surveyed 640 members of the United States Combined Training Association (total membership in 1975 was 3500), of whom 112 had had equestrian injuries; Bixby-Hammett[5] collected data from 160 accident reports filed with United States Pony Clubs district commissioners between 1982 and 1986 (average annual membership, 9270); and Bernhang and Winslett[16] obtained completed surveys from show stewards at 984 of the 1635 horse shows sanctioned by the American Horse Shows Association in 1979. As with the other types of equestrian studies, females were overrepresented among the injured (Table 4). The percentage of persons hospitalized in the two studies reporting hospitalization statistics ranged from 3% to 17%.[5,16] Fractures accounted for 16% to 33% of all injuries, with head injuries ranging from 21% to 34%. Bernhang and Winslett[16] and Bixby-Hammett[5] reported low rates of injury but used different denominators from those used in the emergency department studies, making injury rate comparisons difficult. The study by Bernhang and Winslett[16] was the only one reporting an equestrian-related death. None of the organization studies provided information about long-term impairment.

COMMENT

These studies show equestrian injuries to be more common among girls and young women than among boys and young men. Because the female-male ratio of equestrians is unknown, the predominance of injured females may simply reflect the riding population. Most injuries were the result of falling off a horse. When injuries did occur, they tended to be serious, as shown by the large number of fractures and head injuries reported and the high proportion of persons presenting to emergency departments who required hospitalization (as high as 38%). Although most injuries were those from which children and young adults can reasonably be expected to recover (eg, injury to

Table 3.—Results of Emergency Department Studies

	Williams[12] (N=336)	Danielsson and Westlin[13] (N=119)*	Gierup et al[14] (N=174)*	McLatchie[15] (N=115)	*MMWR*[4] (N=92 763)†
Location	Western United States	Sweden	Sweden	Southwestern Scotland	United States
Study years	1972-1973	1970-1971	1972-1973	1977-1978	1987-1988
% of subjects aged ≤25 y	50‡	75‡	80‡	77	50
% of female subjects	52	87	86	83	60
% of subjects injured owing to a fall	Not reported	90	64	72	Not reported
Major injury site (% of subjects)	Arm/leg (47)	Arm (61)§	Not reported	Arm (42)‖	Arm (30)
% of subjects sustaining a fracture	36	45§	48	Not reported	28¶
% of subjects sustaining head injury	28	10§	11	14	19
% of subjects hospitalized	38	Not reported	17	23	10
Injury rate	Not reported	<1/1000 lessons	0.7/1000 rides	2/1000 riding hours	Not reported

*Riding club members only.
†Estimated number based on a sample of US hospital emergency departments.
‡The oldest person in this subgroup was aged 19 y.
§Injuries due to falls only.
‖Excludes minor injuries (eg, bruises and sprains).
¶Includes persons with dislocations.

Table 4.—Results of Studies of US Riding Organizations

	Mahaley and Seaber[2] (N=112)	Bixby-Hammett[5] (N=160)	Bernhang and Winslett[16] (N=290)
Study years	1975	1982-1986	1979
% of subjects aged ≤25 y	58	100	63*
% of female subjects	90	94	Not reported
% of subjects injured as the result of a fall	Not reported	Not reported	Not reported
Most common injury site (% of subjects)	Not reported	Not reported	Head (34)†
% of subjects sustaining a fracture	33	24	16
% of subjects sustaining head injury	21	Not reported	34†
% of subjects hospitalized	Not reported	17	3
Injury rate	Not reported	3.5/1000 members	0.13/ show day

*The oldest subject in this subgroup was aged 18 y.
†Includes persons with dislocations.

Table 5.—Medical Contraindications and Possible Limiting Factors for Recreational Equestrian Sports[21]

Contraindications

History of cervical fracture or dislocation
Congenital absence of odontoid process of the axis
Temporary paralysis of any cause
Head injury with permanent impairment
Congenital narrowing of spinal canal

Possible Limitations (Evaluate on a Case-by-Case Basis)

Repeated concussions
Brachial injury
Lumbar injury
Herniated intervertebral disk
Recurrent injury to cervical or lumbar ligament(s) or muscle(s)

a limb), a number of head injuries resulted in death and permanent disability.

Severe horse-related injuries can also occur in other settings. A hospital admission study of pediatric farm injuries found that 36% of serious injuries were the result of horse-related activities.[17] There is no *International Classification of Diseases* code for fatalities resulting specifically from horse-related activities; however, from 1979 to 1988, an average of 42 people 24 years old or younger died per year of injuries sustained while riding animals.[18] Many of these deaths may have been due to equestrian activities.

To estimate the risk of injury owing to equestrian activities, injury rates, such as the number of injuries per units of exposure (eg, number of riding hours or total number of rides) must be determined. Despite the differences in how injury rates were estimated in the emergency department and riding organization studies,[5,13-16] the rates of injuries to equestrians were low compared with those for wrestlers (10.7 per 1000 exposures),[19] football players (6.1 per 1000 exposures),[19] track and field participants (5.68 per 1000 hours of exposure),[20] and intercollegiate basketball players (4.5 to 4.8 per 1000 person-hours of exposure).[21]

The studies reviewed used varied sources of data and had significant methodologic limitations. Although equestrian activities have existed for centuries, further research is needed to identify basic risk factors associated with equestrian injuries. For example, the roles of rider age, experience, and training; breed and training of the horse; type of riding activity; supervision; and riding environment in injury causation have not been adequately assessed. Research is also needed to evaluate the effectiveness of equestrian injury prevention measures such as educational programs and use of protective equipment.

Despite the limitations of the studies and the need for more research, we believe several conclusions and recommendations can be made. Horseback riders are at risk for serious and even fatal head injuries.[1-4,8-12,16] Equestrians should wear properly secured hard-shell protective headgear (helmets) lined with expanded polystyrene or similar material when close to or riding horses.[4] Although no studies demonstrate the effectiveness of helmets for this population, hard-shell helmets greatly reduce the risk of head injury to bicyclists[22] and motorcyclists[23] and are likely to be effective for equestrians because of the similar mechanism of injury (falling). The only national equestrian organization that requires protective headgear for all equestrian activities is the United States Pony Club; the American Horse Shows Association and the United States Combined Training Association require protective headgear only for certain types of activities (primarily during jumping events).[24] Both the American Academy of Pediatrics and American Medical Association have endorsed the use of protective headgear for equestrians.[25,26] Although many types of protective headgear are available, only those that meet the standards of the American Society for Testing Materials should be used.[27]

Horseback riders need appropriate training and education about how to ride. They must be taught proper techniques for mounting and dismounting a horse, for stopping a horse, and for using their extremities and reins to control a horse's direction and speed. Children and young adults who cannot perform these actions should only ride under the direct visual supervision of a well-trained and experienced rider. Children younger than age 6 years should not ride a horse independently, according to Margaret Taylor, chairman of the United States Pony Club safety committee (oral communication, November 1991). Riders should receive training from experienced instructors who emphasize safety and who have completed an accredited horse-safety course.[4]

Although falls are the most common mechanism of injury, other mechanisms include kicks, bites, crushing injuries, trampling, being dragged along the ground with a foot trapped in a stirrup, and collisions with fixed objects.[3,4,11] Children and young adults should be very alert and careful when on or near horses.

Riding equipment (tack) should be inspected regularly and replaced if worn. Saddles should fit snugly and should be checked to ensure that they will not slip while riding; stirrups should be the appropriate size for the rider. All riders should wear heeled, smooth-soled footwear with adequate ankle support and avoid loose-fitting clothes that may snag on tree limbs or other objects when riding. Safety vests may also be considered, although there is no evidence that they reduce the risk of chest or rib injuries.[28]

Table 5 lists medical contraindications and potentially limiting factors for recreational horseback riding.[27] Well-controlled idiopathic epilepsy or insulin-dependent diabetes mellitus are *not* indications for restrictions. Pediatricians must counsel patients involved in equestrian activities to become thoroughly knowledgeable about the hazards of the sport, to understand the importance of appropriate training and safety practices, and to wear protective headgear when riding or working around horses.

As with the campaign to increase bicycle safety, pediatricians can play a major role in community, state, and national efforts to reduce equestrian injuries.[29] Equestrian organizations with safety committees can benefit tremendously from a physician's input. If local or state organizations have no safety committees, pediatricians can play a key role by presenting information about injury prevention to members of the boards of directors. Pediatricians and other health professionals, either independently or through local, state, and national medical organizations, should encourage riding stables, riding clubs, and equestrian organizations at all levels to require protective headgear for riders. At all levels, pediatricians can help reduce the risk of injury and death due to equestrian activities.

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School-based Adolescent Health Care

Review of a Clinical Service

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• *Objective.*—To provide recommendations regarding the establishment and maintenance of school-based clinics, based on analysis of data from a clinic located in a New York City high school.

***Design.*—Review of demographic, medical, and psychosocial data collected during student visits.**

***Subjects.*—During 2½ years, 1283 students were seen. The students were 53% girls and 47% boys; 65% black and 25% Hispanic; and 65% grades 9-10 and 35% grades 11-12.**

***Results.*—There were 7920 visits. Visits were for acute or chronic medical problems (44%), physical examinations and immunizations (25%), gynecologic or sexuality-related issues (17%), and mental health concerns (14%). Psychosocial characteristics of the 378 students who enrolled during the 1989-1990 academic year indicated that only 27% lived with both natural parents, 55% were foreign-born, 37% had repeated a grade at least once, 44% were sexually active, 13% drank alcohol, and 14% had past or present suicidal ideation.**

***Conclusions.*—These data demonstrate that a school-based clinic can be involved in the management of a wide range of health care needs for large numbers of at-risk youth. In addition, school-based clinics can serve as a major site for the teaching of medical students and residents, and as a valuable resource for clinical research.**

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During the past decade, school-based clinics have been established in more than 150 American high schools to manage the multitude of medical and psychosocial problems faced by present-day adolescents, especially those living in inner-city environments.[1] Preliminary reports have been encouraging, demonstrating that health clinics for teenagers can function effectively in the school setting and the services they provide can affect specific problems such as teen pregnancy.[2-9] On the basis of these findings, several medical organizations, including the American Medical Association and the Society for Adolescent Medicine, have published position papers supporting the growth of school-based clinics throughout the country.[10,11] In addition, the American Academy of Pediatrics has established access to care as a current priority, and school-based clinics offer a potential means of providing health services to those otherwise deprived of high-quality health care.

School-based clinics have been described by many as "sex clinics," with the impression that they direct their primary efforts to sexually related issues and actually promote sexual activity among teenagers. This misconception continues in many communities despite preliminary reports that sexually related and reproductive problems account for only a small percentage of staff activity and student visits in school-based clinics.[1,12,13] Nonetheless, the controversy about the role such clinics play regarding sexuality has obscured the far more important question of the efficacy that school-based clinics have in meeting the total medical and mental health needs of the students they serve.[14-16] Further, optimal management of the issue of confidentiality in regard to both school personnel and parents is still being explored. Moreover, the long-term financial viability of this system of health care provision remains a dilemma.

The Division of Adolescent Medicine at North Shore University Hospital—Cornell University Medical College in Manhasset, NY, established a school-based clinic in a New York City high school in early 1988. During the subsequent 2½ years, more than 1200 students made approximately 8000 visits to this high school clinic. To document the needs of the students and the health care they have required, we performed a detailed review of the demographic and medical data collected during all student visits since the inception of the clinic. What follows are results of that review, with an emphasis on those aspects necessary for the pediatric community to evaluate the desirability of continued growth of school-based clinics.

MATERIALS AND METHODS

Facility Description

In 1986, our division responded to a request for proposals put forth by the Robert Wood Johnson Foundation for the establishment of 20 school-based clinics in high schools throughout the United States. Exploration with the New York City Department of Health led us to Far Rockaway High School, which was con-

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Table 1.—Enrollment Data for School-based Clinic, February 1988 Through June 1990

	February 1988 to June 1988	July 1988 to December 1988	January 1989 to June 1989	July 1989 to December 1989	January 1990 to June 1990
New students enrolled in clinic	335	317	195	273	153
Total visits to clinic	855	1276	1779	1778	2232
Students discharged from clinic	. . .	84	61	228	95
Total enrollment in clinic	335	578	794	839	897
Approximate student population in school	1800	1900	1800	1600	1500
Percentage of school's students enrolled in clinic	19	30	44	52	60

sidered to have students with major unmet health needs and a principal who was sympathetic to a school-based health facility. The school is located in an isolated but urban section of Queens, NY, with an enrollment of approximately 2000 students. The application, which was developed with the guidance of a Community Advisory Board, was accepted for funding in July 1987, and the clinic was opened for student visits in February 1988.

The clinic provides health services to the students from 8 AM to 4 PM on all days that the school is open, including summer sessions. The clinic is located on the first floor of the school, across from the Dean's office, and between the boys' and girls' gyms, and is divided into examining rooms, offices, laboratory space, an emergency area, and a waiting room. Each student enrolled in the clinic must have a consent form signed by a parent or legal guardian. This is standard for all clinics in The Robert Wood Johnson Program and the New York City school system. The consent form allows the parent or guardian to choose specific services that can or cannot be provided to each child. Students are not charged out-of-pocket fees, but insurance and Medicaid information is sought so that third-party payments can be applied for when appropriate. Clinic charts are maintained separately from school health records; health service personnel have access to both sets of records, while school personnel have access only to the latter.

The clinic was initially staffed by (1) a pediatric nurse practitioner, who has served as Clinic Director and has provided approximately half of the clinical services; (2) attending physicians and fellows from the Division of Adolescent Medicine, who rotate to cover the clinic 3 to 5 hours daily; (3) two health aides provided by the New York City Board of Education, who are responsible for recordkeeping of required health screening, emergency services for both enrolled and nonenrolled students, reception, triage, and basic, on-site screening tests; (4) a para-aide provided by the school, who assists the health aides; (5) a health resource coordinator provided by the New York City Department of Health, who provides education in the classrooms and clinic and performs referral and follow-up services; and (6) a psychologist and psychology graduate students, collectively present about 50% of the time. In March 1990, funding was received from the New York City Department of Mental Health and Mental Retardation for a full-time social work position.

Data Collection

Students were seen in the school-based clinic either as scheduled appointments or as walk-ins. Each new student received a comprehensive health evaluation. This included a patient and family medical history; a psychosocial history, including school performance and relationships with family and friends; a medicosocial history, including issues related to sexuality, substance abuse, eating habits, accidents, and suicidal ideation; a complete physical examination, including a gynecologic examination for those girls who are sexually active or have gynecologic complaints; and laboratory screening tests (namely, hemoglobin, urinalysis, and tuberculosis screening for all patients; Papanicolaou smear, culture for *Neisseria gonorrhoeae*, and *Chlamydia* testing for sexually active girls; and gonorrhea and *Chlamydia* testing for symptomatic boys or those with multiple partners).

Information obtained from all health evaluations is maintained in patient charts and compiled on a regular basis. The data collection was performed manually from February through June 1988, and by computer from July 1988 through June 1990. Medicosocial history was added to the computer program in July 1989. Additional information is gathered for each visit (including reason for visit, services provided, diagnosis, referrals, and time spent), and these data also are assembled by computer. All data were tabulated in July 1990 for the initial 2½ academic years of the program.

The 1283 students made a total of 7920 visits to the school-based clinic. The clinic had an additional 250 parental consent forms on file for students still in the school who had not yet come to the clinic for any visits. As noted in Table 1, which presents data for each 6-month period, steady increases in enrollment each semester, coupled with concomitant decreases in total student population in this particular high school, resulted in significant increases in the percentage of students enrolled, from 19% in June 1988 to 60% in June 1990.

RESULTS

Demographic Data

Demographic characteristics of the overall student population and of those who visited the clinic are presented in Table 2. In a school with an equal number of boys and girls, 53% of initial visits to the clinic and 67% of total visits were by girls. Approximately two thirds of the students are black; 65% of initial visits to the clinic and 74% of all visits were by black students. Data by grade and age reveal that both the school and clinic enrollment decreased from grade 9 to grade 12, and that patient visits were greatest among those aged 16 and 17 years.

Student Visits to the School-based Clinic

As expressed by the students' "chief complaint," the 7920 visits to the clinic reflected a wide range of medical, gynecologic, and mental health needs (Table 3). More than two thirds of visits were for acute or chronic medical problems (44%) or physical examinations and immunizations (25%), while fewer than one third were for gynecologic or sexuality-related issues (17%) or mental health concerns (14%). Length of visit with the practitioners was

Table 2.—Demographic Characteristics of School-based Clinic Patients

	Initial Visits, % (n=1283)	Total Visits, % (N=7920)	School Enrollment, % (n=1916)
Sex			
F	53	67	50
M	47	33	50
Race			
Black	65	74	66
Hispanic	25	20	23
Other	10	6	11
Grade			
9	38	. . .	31
10	27	. . .	28
11	22	. . .	22
12	13	. . .	19
Age, y			
13-15	44	29	. . .
16-17	44	57	. . .
18-20	12	14	. . .

Table 3.—Student Visits to the School-based Clinic

	No. (%)
Student's reason for visit (N=7880 visits)	
Acute or chronic medical problem	3468 (44)
Physical examination or immunization	1975 (25)
Gynecologic or sexuality-related issue	1310 (17)
Mental health concern	1127 (14)
Primary diagnosis as a result of visit (N=7920 visits)	
Well adolescent	1497 (19)
Sexuality-related	1092 (14)
Mental health	985 (12)
Infection	931 (12)
Injury/orthopedic	874 (11)
Gynecologic	486 (6)
Neurology/ophthalmology	501 (6)
Gastroenterology/genitourinary	367 (5)
Endocrine/obesity	348 (4)
Dermatology	284 (4)
Cardiology/pulmonary	219 (3)
Hematology	174 (2)
Dental	86 (1)
Allergy	76 (1)

less than 10 minutes for 33% of visits, 10 to 20 minutes for 41% of visits, and more than 20 minutes for 26% of visits. Specific diagnoses recorded for each visit by the clinic staff and summarized in Table 3 were as follows:

1. Well-adolescent care represented 20% of all diagnoses. This included students who presented for required physical examinations for sports participation, working papers, or school entry and those who required updated immunizations (either completion of a primary series, 10-year tetanus update, or second measles, mumps, and rubella immunization).

2. Sexuality-related care represented 14% of all diagnoses. During the course of 2½ years, when appropriate and not restricted by parental consent, students were routinely counseled about contraceptive services and counseled and screened for sexually transmitted diseases. There were 455 visits for contraceptive services, 218 visits for sexually transmitted disease diagnosis and/or treatment, and 357 visits for pregnancy testing. Of the latter, 125 students were in fact pregnant; 10% (n=12) of these pregnancies ended in miscarriage, 55% (n=69) were terminated, 33% (n=42) resulted in delivery, and 2% (n=2) were not available for follow-up. All pregnant students were referred to other facilities for gynecologic or obstetric care after appropriate diagnosis and counseling were performed in the school-based clinic.

3. Twelve percent of all diagnoses were for mental health concerns. This included students seen initially for medical problems and in regular counseling sessions by the mental health staff for school or family problems, as well as students treated acutely for depression or suicidal ideation. The number of mental health visits has increased steadily over time, as we have become better known and more accepted in the school, and the staff has grown to accommodate this major need.

4. Twelve percent of visits were for a range of infections, and 11% for injuries or orthopedic conditions. These two categories represent the majority of patients seen for acute medical concerns (usually as unscheduled visits), most of which resulted in the student returning to class after receiving appropriate care or reassurance.

5. Gynecologic concerns represented 6% of all diagnoses, divided equally between those girls seen acutely for dysmenorrhea (who received medication and returned to class) and those girls who were evaluated for more significant gynecologic concerns (including amenorrhea or oligomenorrhea).

6. Specific medical diagnoses accounted for the remaining 25% of visits. These ranged from students who presented with the acute onset of headaches, abdominal pain, or a toothache; those diagnosed with anemia, a heart murmur, or myopia; those with known chronic diseases, including asthma, inflammatory bowel disease, sarcoidosis, and Graves' disease; and those treated for obesity, acne, and allergies.

Psychosocial and Medicosocial Characteristics

Psychosocial and medicosocial data were obtained at the start of the 1989-1990 academic year, through semistructured interviews, for the 378 students who underwent a complete evaluation during the 1989-1990 academic year. As noted in Table 4, large numbers of students were foreign-born and did not consider English to be their first language. Further, fewer than one third lived with both natural parents and many had changed their address within the past year. Many students indicated that their parents had not graduated from high school and more than one third of both mothers and fathers were not employed (or the student did not know whether the parents were employed). Almost one third of students were enrolled in special programs (ie, special education, career directed, or drop-out prevention), and more than one third had repeated at least one grade. Also, approximately one third of students did not have a group of friends and/or did not have a best friend.

Medicosocial issues revealed by these 378 students (mean age, 15.6 years) included substance use, sexual activity, and mental health problems (Table 5). Occasional or frequent use of alcohol and cigarettes were reported by 13% and 6% of students, respectively, while few students admitted to occasional or regular use of marijuana and none admitted to any use of crack or cocaine. In contrast,

Table 4.—Psychosocial Characteristics of School-based Clinic Enrollees, 1989-1990 Academic Year (n=378)

	No. (%)
Personal background	
Living in United States <1 y	97 (26)
Born in the United States	170 (45)
First language English	278 (74)
Living arrangements	
Lives with both natural parents	103 (27)
Lives with father	144 (38)
Lives with mother	265 (70)
Lives at same address <1 y	152 (40)
Parents' education and employment	
Mother graduated high school	192 (51)
Father graduated high school	175 (46)
Mother employed	250 (66)
Father employed	243 (64)
School and friends	
In special programs	110 (29)
Repeated grade at least once	134 (35)
Does not have a best friend	149 (39)
Does not have a group of friends	117 (31)

Table 5.—Medicosocial Characteristics of School-based Clinic Enrollees, 1989-1990 Academic Year (n=378)

	No. (%)
Substance use	
Occasional/frequent use of alcohol	47 (12)
Occasional/frequent use of cigarettes	22 (6)
Occasional/frequent use of marijuana	4 (1)
Occasional/frequent use of cocaine/crack	0
Sexual activity	
Has been sexually active	168 (44)
Sexually active, younger than age 15 y	84 (22)
Sexually active, younger than age 13 y	39 (10)
One or more pregnancies	19 (5)
Mental health	
Depressed "most of the time"	18 (5)
Suicidal gesture at least once	21 (6)
Suicidal ideation (past or present)	54 (14)
Has received therapy	49 (13)
Would benefit from therapy	112 (30)

44% of students reported that they were sexually active, with half of these students initiating sexual intercourse before age 15 years and one quarter before age 13 years. Among those who were sexually active, 55% reported one or two lifetime partners, 25% reported three to five lifetime partners, and 20% reported six or more lifetime partners; 55% of sexually active students indicated they had never used birth control, and 30% indicated they used birth control at last intercourse. Condoms had been used at some time by 89 (53%) of the 168 sexually active boys or partners of sexually active girls, 18 girls had used oral contraceptives, and eight girls had tried other barrier methods (eg, diaphragm, sponge, or foam). Seventeen students indicated they had been involved in one pregnancy, two girls had been pregnant twice, and seven students (five girls and two boys) had a living child. Mental health concerns included significant depression, as well as suicidal ideation and gestures. While 13% had received counseling or therapy at some time in the past, an additional 30% were judged to require such help.

Table 6.—Referrals, Insurance Status, and Prior Medical Care of School-based Clinic Patients

	No. (%)
Referral source (n=1206)	
Self/peer	439 (36)
Teacher	311 (26)
Other staff	401 (33)
Parent	55 (5)
Routine source of medical care (n=999)	
Physician/clinic	616 (62)
Emergency department	89 (9)
No regular source	294 (29)
Most recent medical care (n=1057)	
Within 1 y	691 (65)
1-2 y	222 (21)
>2 y	144 (14)
Insurance status (n=1235)	
Medicaid	173 (14)
Private insurance	248 (20)
No coverage	814 (66)

Referrals and Financial Considerations

Referrals to the school-based clinic were divided among students, teachers, and other school staff (Table 6); few referrals were initiated by parents despite initial outreach efforts provided by the Parent Association. On their initial visits, 62% of students indicated a specific physician or clinic whom they generally had visited for their health care, while 38% used an emergency department or had no regular source of care. Contrary to initial expectations, only 14% had Medicaid and 20% had private insurance; 66% of students had no medical insurance coverage. This resulted in total reimbursements from third-party payers for all 7920 visits of approximately $30 000 during the first 2½ years of clinic operations.

Since two thirds of the students had no insurance, referrals from the clinic to other health facilities and subspecialists were judiciously planned to fit with financial realities. There were a total of 586 referrals: 51% (n=299) were for medical care, 26% (n=152) for dental care, 9% (n=53) for roentgenography, and 8% (n=47) for mental health services. The remaining 6% (n=35) were for education, family planning, or social services. In total, 47% of all referrals were kept by the students. The best completion rates were for those services for which compliance did not depend solely on the students and their families. These included social service referrals for suspected child abuse, education services when the appropriate school personnel were immediately contacted by clinic staff, and mental health referrals, which were psychiatric emergencies such that the student was transported to a nearby emergency department. The poorest completion rates were for medical and dental services.

COMMENT

Although most adolescents receive their medical care in doctors' offices and hospital clinics,[17] it has been apparent, since the inception of Adolescent Medicine as a subspecialty of pediatrics in the 1950s, that many of the adolescents who are most at risk do not avail themselves of necessary care. Several attempts have been made over time, including walk-in clinics in the 1960s and hospital satellite clinics in the 1970s, to provide needed care in settings more available and conducive to adolescents. The growth of school-based clinics through the 1980s is an extension of this trend, with more than 150 clinics functioning in high schools at present.[1] To continue, school-based clinics will have to prove they can be functional, efficient, and financially viable; they can rise above the controversies that often accompany their development; and they have an impact on the students and schools that they serve.

Before this report, there have been few data to document the range of problems that can be managed in a school-based clinic. The Center for Population Options publishes a yearly report that updates the growth of school-based clinics nationally, the services offered by these clinics, and a demographic profile of the students who visit the clinics.[1] The most recent national demographic data demonstrate that students who visit the clinics are 57% female and 43% male, and are 31% white, 44% black, 18% Hispanic, 3% Asian, and 5% other. The Center for Population Options data do not indicate, however, how the services of the clinics nationally are used. Most reports published to date have concentrated on their use for reproductive and sexually related health services.[2-4,6-9] Only in several recent foundation reports[12,13] has the concept that school-based clinics provide comprehensive care for a wide range of needs begun to be clearly delineated.

Establishment and Growth of the School-based Clinic

The school-based clinic described herein was established with the cooperation and support of the New York City Department of Health, the New York City Board of Education, two supporting hospitals, and the Robert Wood Johnson Foundation. Such cooperation between public and private agencies has been crucial in the development of many successful school-based clinics, from both a financial and staffing point of view. Further, the clinic received backing from the principal of the high school, the local community, and the Parent Association, and this support is equally important for the success of a school-based clinic. It is also important to realize that it may take more than 1 year of planning before a functional school-based clinic can be established.[1-4,12-16]

Students were first seen at the school-based clinic in February 1988. Most of the 335 students who registered during the first semester of clinic operations enrolled for required physical examinations rather than for specific medical, gynecologic, or mental health concerns, and they represented 19% of the total student body. During the following 2 years, the number of new registrants at the clinic was significantly greater than the number of registered students who left the school, such that the 897 active students enrolled in June 1990 represented 60% of the student body. A goal of 60% to 70% appears to be standard for most school-based clinics, as some students and families will not choose to receive health care in the school setting.[1,12,13] Thus, the school authorities should be prepared to provide an alternative means of emergency care for those not enrolled in the school-based clinic. In the school described herein, the same health aides who assisted in the clinic also provided emergency care to students not enrolled in the clinic, and the health resource coordinator provided referrals for medical and counseling services to all students.

The 1283 students enrolled in the clinic during its first 2½ years made a total of 7920 visits. Some students were seen only once, others multiple times. Clinic visits grew from 855 visits the first half-year to more than 3000 the second year, and more than 4000 the third year. This growth requires support from students, parents, and school personnel, which can only be forthcoming if the needs of all are carefully balanced. Issues of confidentiality and consent are crucial in the development of trusting relationships in the school setting. We believe it is important to maintain two sets of student records: confidential medical records for clinic personnel, and separate records for immunizations and mandated screening that are open to school personnel. We also believe that the use of parental consent forms has been beneficial in the care of our registered students, though we are concerned that this requirement may have prevented other students from registering for health care.

Background Characteristics of the Students

As a matter of policy, school-based clinics are being placed in schools where the students are deemed to be most in need of medical services, and where teenagers do not have access to adequate medical care. The data demonstrate that the students in the school described herein meet all the criteria. The students in the school and clinic are predominantly black and Hispanic, many are foreign-born and have recently moved, and barely one quarter are living with both natural parents. Fully one third are in special programs and/or have repeated a grade at least once, and a similar number report not having a best friend and not having a group of friends. Certainly, these are background factors signifying youth who are at risk. Although many students report having a source of medical care and having been seen by a physician within the past year, there is evidence that the range and depth of medicosocial problems faced by many youth may not be treatable in the standard medical practice, even in suburban environments.[18-20] This problem is obviously enhanced greatly for inner-city youth who often lack adequate insurance coverage.[21,22] It is our impression that most of the youth attending this school-based clinic who indicated that they had a regular source of health care have, in fact, used these sources of care only sporadically and for specific issues; these same students generally have not been willing to return to their "regular" doctors for most of the problems we have diagnosed and treated.

The medicosocial risk factors described herein also portray adolescents at risk, although the data are less dramatic than might have been expected. A small percentage of students indicated they drank alcohol or smoked cigarettes, while almost none admitted to marijuana or cocaine use. Because we suspected that the students may not have been willing to provide truthful answers, we performed a study to test the validity of these data.[23] Using a statistical technique entitled "Randomized Response," we determined that the students were engaging in slightly more alcohol and cigarette use than they reported on interview, but that few were involved with either marijuana or cocaine. Similar data were reported recently in a study of substance use patterns in New York State, prompting a conclusion that those urban students who remain in school are participating in less drug or alcohol use than is commonly believed.[24]

At the time of initial evaluation, fewer than half of the students reported being sexually active. However, among these, some indicated they had intercourse at very young ages (including a group of boys who were sexually active before age 10 years). Most did not use appropriate birth control, many had large numbers of partners, and several girls had been pregnant. Similar data, which have been reported elsewhere,[25,26] indicate that sexual activity is a high-risk behavior for "only" about half of the youth in this report. Of note is that 44% of students were age 13 to 15 years at the time of initial evaluation, and although many report not being sexually active at that time, our experience is that many additional students will seek reproductive health services before graduation. Similarly, mental health concerns were noted in many of the students registered in the clinic; for some, the problems were severe, including long-standing family problems, depression, and suicidal ideation or gestures. Although the literature emphasizes the problems of adolescent suicide predominantly among white teenagers,[27,28] our data indicate that suicidal ideation is an equally significant problem in a high school where the majority of students are black and Hispanic, and the resources for treating these problems may be extremely limited.

Visits to the School-based Clinic

While much of the early literature concentrated on the effect of school-based clinics on adolescent pregnancy,[2-9] we have found that our school-based clinic is used for a variety of problems. Sexuality-related diagnoses account for only 14% of all student visits. Indeed, approximately two thirds of visits are for medical concerns, including acute and chronic problems and health maintenance issues, while the remaining one third are for gynecologic or mental health concerns.

Well-adolescent care was the entrée to the clinic for most students, especially during the first year of the program. Students who require physical examinations for sports, working papers, or school entry are more likely to "try out" a new clinic and to return a parental consent form than those with problems. As a clinic's reputation in a school grows, however, the range of initial concerns broadens.

Immunization update is especially important as many adolescents may have incomplete immunization histories for a variety of reasons. It was common to find students who had received no immunizations since early childhood, foreign students who had incomplete immunizations on entry into the country, and students who required a second measles, mumps, and rubella immunization. We also performed tuberculosis screening on all students, and administered prophylactic tuberculosis therapy to more than 30 students during the 2½ years.

Acute medical concerns, including infections, accidents, and dysmenorrhea, account for a significant number of visits. These may be treated on site, with the student then returning to class. We believe that this is an important role for a school-based clinic, that is, to potentially assist in lowering the astronomical absentee rates currently reported in most city schools.[29] Detection and treatment of chronic medical problems may similarly have a positive effect on both the absentee and drop-out rates in the schools, as can the provision of both sexuality-related and mental health services. Further study will be required to determine whether these important, potential benefits are in fact realized in this and other schools with clinics.

Financial Considerations

Our clinic receives monetary support from the Robert Wood Johnson Foundation ($100 000 per year for a period of 6 years), with additional contributions of approximately $100 000 per year provided by the sponsoring hospital (North Shore University Hospital—Cornell University Medical College) and other outside agencies, mostly for staffing. Other public and private sources have been helpful in partially covering such expenses as laboratory tests and roentgenography for students without health insurance. It was disappointing and worrisome to discover that two thirds of the students were not covered by either private insurance or Medicaid, and this accounts for the minor financial contribution received through third-party reimbursement. It is apparent that most of the students have parents employed in jobs that do not provide insurance; this problem of the "working poor" of course is not unique to the school-based setting.[21,22] We believe that the lack of insurance coverage is partially responsible for poor compliance rates of medical and dental referrals, even among those who say they have a regular source of care. Undoubtedly, inadequate reimbursement will represent the greatest hurdle for the growth of the school-based clinics throughout the country.

The School-based Clinic as an Academic Program

Although not reflected in the data presented, the accessibility to large numbers of adolescents provided by a school-based clinic allows for the development of clinical research and for provision of medical education to both adolescents and medical trainees. We have worked with school personnel on a yearly health screening and education program for all (enrolled and nonenrolled) students, have developed a self-esteem program for all students entering 9th grade, have provided teacher training and classroom lectures on health-risk behaviors, and have organized health fairs for the school and the community. We have also used the school-based clinic site for the education of medical students, pediatric and internal medicine residents, nursing students, and psychology graduate students, and with them have begun to study the health behaviors of the students in the school. Activities such as these all have the potential for research, and our involvement in the school has already resulted in presentations at national meetings and publication of scientific articles. Teaching and research are both important in fulfilling the full potential of a school-based clinic program.

Staffing Issues

There is no one set staffing pattern for a school-based clinic. The staffing for our clinic was determined by available funding and perceived need. The New York City Department of Health and Board of Education reassigned staff already addressing health issues in the school. This reassignment avoided a potentially competitive and threatening relationship between existing health-related services and those staff members specifically recruited for the clinic, and provided a "critical mass" of personnel for the program. The result has been a clinic staff that functions smoothly despite the differing agendas and requirements of the multiple agencies involved.

Flexibility is the key when determining clinic schedules for the medical and mental health staff. Our initial efforts to provide more services toward the end of the school day and after school quickly proved unsuccessful. Our experience has been that the bulk of the clinic services are used during the school day, with lunch times and gym classes being the preferred times for scheduled appointments. The after-school times are used on a very limited basis, as they compete with student jobs, team sports, and responsibilities at home.

Difficulties and Frustrations

Along with the excitement generated by this project comes a set of problems. These problems fall into two categories: day-to-day operations and long-term funding. The first set of problems are largely related to operating a health service in a nontraditional environment with limited support services. It is not unusual to find that valuable staff time is spent on tasks such as housekeeping, equipment maintenance, and the ordering and transporting of supplies. Secondly, the difficulties in securing long-term funding have become particularly acute, given the growing competition for scarce resources. As has been noted, this project cannot currently support itself on patient-generated revenues, and this is consistent with the national experience.[30] This finding emphasizes the need for a long-term stable source of funding and the development of methods to overcome the constraints placed by traditional funding sources, such as Medicaid and private insurance.

The accomplishments as well as the problems of school-based clinics have been recognized by public policy analysts, legislators, and state agencies. Efforts to support the financing of clinics, including increasing access to public funds, are being discussed. We hope these discussions will be successful in ensuring the future of school-based clinics.

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Antipyretic Efficacy of Ibuprofen vs Acetaminophen

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• ***Objective.***—**To compare the antipyretic efficacy of ibuprofen, placebo, and acetaminophen.**

Design.—**Double-dummy, double-blind, randomized, placebo-controlled trial.**

Setting.—**Emergency department and inpatient units of a large, metropolitan, university-based, children's hospital in Michigan.**

Participants.—**37 otherwise healthy children aged 2 to 12 years with acute, intercurrent, febrile illness.**

Interventions.—**Each child was randomly assigned to receive a single dose of acetaminophen (10 mg/kg), ibuprofen (7.5 or 10 mg/kg), or placebo.**

Measurements/Main Results.—**Oral temperature was measured before dosing, 30 minutes after dosing, and hourly thereafter for 8 hours after the dose. Patients were monitored for adverse effects during the study and 24 hours after administration of the assigned drug. All three active treatments produced significant antipyresis compared with placebo. Ibuprofen provided greater temperature decrement and longer duration of antipyresis than acetaminophen when the two drugs were administered in approximately equal doses. No adverse effects were observed in any treatment group.**

Conclusions.—**Ibuprofen is a potent antipyretic agent and is a safe alternative for the selected febrile child who may benefit from antipyretic medication but who either cannot take or does not achieve satisfactory antipyresis with acetaminophen.**

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Fever is one of the most common signs of intercurrent infectious illness in childhood and frequently leads to the administration of antipyretic medication. Acetaminophen has been the most widely used antipyretic medication for children in the United States since the early 1980s, when aspirin use during febrile illnesses was associated with increased risk of Reye's syndrome.[1] Since 1989, ibuprofen, a proprionic acid–derivative, nonsteroidal anti-inflammatory drug, also has been available in the United States as a prescription antipyretic medication for children aged 6 months to 12 years. Ibuprofen has been available over the counter for individuals aged 12 years and older since 1984. Several studies[2-10] have documented the antipyretic efficacy of ibuprofen in children suffering from a variety of febrile illnesses. We report the results of a double-blind, placebo-controlled study comparing the antipyretic effect of ibuprofen and acetaminophen in children aged 2 to 12 years during acute febrile illnesses.

See also p 626.

PATIENTS AND METHODS

Otherwise healthy children aged 2 to 12 years presenting to the emergency department or admitted to the hospital because of acute intercurrent febrile illness were enrolled in the study after informed consent was obtained from at least one parent or legal guardian and with assent of the child, when appropriate. No child was hospitalized for the purpose of the study. Children who did not require hospitalization for management of illness were treated and observed in the emergency department for the duration of the study and then released. The protocol was approved by the Children's Hospital of Michigan Institutional Review Board.

Patients were required to have an oral temperature of 38.3°C or higher for at least 1 hour before enrollment. Exclusion criteria included ingestion of an antipyretic medication within 8 hours before starting the study; administration of an antibiotic before enrollment; administration of intravenous fluids during the study; hypersensitivity to aspirin or other nonsteroidal anti-inflamatory drugs; history of a pathologic gastrointestinal condition; renal, hepatic, cardiac, malignant, or hematopoietic disease; and asthma, diabetes, dehydration, or seizures associated with the present illness. Patients were allowed administration of one initial oral dose of an antibiotic during the 8-hour observation period if medically indicated. A venous blood sample obtained before administration of the study drug was assayed to confirm absence of salicylate and acetaminophen.

Patients were randomly assigned to receive a single dose of ibuprofen (7.5 or 10 mg/kg), acetaminophen (10 mg/kg), or placebo to be administered orally. A double-dummy, double-blind study design was used. Acetaminophen and acetaminophen placebo solutions were used with ibuprofen and ibuprofen placebo suspensions. The acetaminophen and acetaminophen placebo solutions were identical in taste and appearance, as were the ibuprofen and ibuprofen placebo suspensions. Each patient received three preparations, at least two of which were placebos. For example, patients randomized to receive 10-mg/kg ibuprofen therapy were given a 20-mg/mL suspension in a volume that delivered 10 mg of ibuprofen per kilogram as well as a placebo suspension in a volume equivalent to 7.5 mg of ibuprofen per kilo-

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Table 1.—Demographic Comparison of Treatment Groups*

Demographic Characteristic	Ibuprofen, 7.5 mg/kg (n=12)	Ibuprofen, 10 mg/kg (n=8)	Acetaminophen, 10 mg/kg (n=8)	Placebo (n=9)
Age, y†	5.6±2.7	6.8±2.8	5.3±3.4	5.8±2.7
Baseline temperature, °C†	38.9±0.3	38.9±0.3	39.0±0.6	38.9±0.4
Race, black/white	12/0	8/0	6/2	9/0
Sex, F/M	8/4	6/2	7/1	6/3
Use of antibiotics, yes/no	4/8	2/6	2/6	4/5

**P* values were not significant among any groups for any demographic characteristics.
†Values are means±SDs.

Table 2.—Treatment Failures

Patient No.	Time After Dose, h	Maximum Temperature Change, °C	Treatment
1	6.0	−1.7	Acetaminophen
2	5.0	−0.9	Acetaminophen
3	2.0	+0.6	Placebo
4	2.0	−0.3	Placebo
5	1.0	+0.4	Placebo
6	1.0	+0.3	Placebo

gram and a placebo solution equivalent to 10 mg of acetaminophen per kilogram. Patients receiving acetaminophen were given two doses of placebo in volumes equivalent to 10 and 7.5 mg of ibuprofen per kilogram and an acetaminophen solution in a volume that delivered 10 mg of acetaminophen per kilogram. Patients receiving placebo were given two doses of ibuprofen placebo suspension in their appropriate volumes and the appropriate volume of acetaminophen placebo. Patients, parents, and health care personnel were blinded to treatment assignment.

Oral temperature was measured twice during the hour before the study medication was administered, 30 minutes after dosing, and 1, 2, 3, 4, 5, 6, and 8 hours after dosing. At each interval, temperatures were measured twice using an electronic thermometer (model 2000, IVAC, San Diego, Calif). The average of duplicate measurements at each interval was used for data analysis. Treatment failure was defined as either a temperature increase of 0.55°C above the baseline temperature or an absolute temperature greater than 40°C at any time during the 8-hour observation period. Patients who fulfilled these criteria anytime during the observation period were administered acetaminophen (10 mg/kg). For data analysis, the last recorded temperature before receiving acetaminophen was assumed to be the temperature for the subsequent intervals. Acetaminophen also was administered to children who required additional antipyretic medication after the 8-hour study period.

Antipyretic response was expressed as hourly oral temperatures (°C), percentage decrease in temperature from baseline, and area under the curve (AUC) of percentage decrease of temperature vs time. Percentage decrease in temperature from baseline was defined as the difference from baseline temperature divided by the difference between baseline temperature and normal temperature (37°C) multiplied by 100. Temperature changes within patients and between treatment groups were analyzed using repeated-measure analysis of variance. Temperature served as the repeated measure, with nine levels, and treatment as the nonrepeated independent variable, with four levels. Mean AUCs for percentage decrease in temperature over time of the different treatment groups were compared using the Mann-Whitney test. Discrete variables were tested using Fisher's Exact Test. An $\alpha \leq .05$ was considered significant.

Patients were monitored during the 8-hour observation period for adverse effects, including symptoms, abnormalities in vital signs, changes in physical findings, and abnormal laboratory findings. A follow-up telephone call was made 24 hours after the study to identify adverse effects that may have occurred after the 8-hour observation period.

RESULTS

Thirty-eight children were enrolled in and completed the study. Data from one patient who was moderately dehydrated and received intravenous fluid during the study were excluded from analysis because of the possibility that dehydration or administration of intravenous fluid may have altered the temperature course. That patient received 10-mg/kg ibuprofen therapy. Data from the remaining 37 patients were included in the analysis. Eight children received 10-mg/kg ibuprofen therapy; 12, 7.5-mg/kg ibuprofen therapy; eight, acetaminophen; and nine, placebo. No significant difference was detected between treatment groups with respect to age, baseline temperature, racial distribution, sex distribution, or receipt of a single dose of oral antibiotic (Table 1). The predominance of black children in the study sample reflects the ethnic composition of patients receiving care at the emergency department of the Children's Hospital. Diagnoses were as follows: fever without apparent focus of infection (eight children); herpetic stomatitis (one child); otitis media (seven children); acute pharyngitis (10 children); pneumonia (three children); acute sinusitis (one child); and viral upper respiratory tract infection (seven children). There was no statistical bias in the distribution of diagnoses among the four treatment groups. None of the children had detectable concentrations of acetaminophen or salicylate in plasma before receiving the study medication.

Six patients fulfilled criteria for treatment failure; two received acetaminophen and four received placebo. The two acetaminophen-treatment failures occurred at 5 and 6 hours after dosing and followed a modest temperature decrement, whereas the placebo-treatment failures occurred between 1 to 2 hours after dosing, with no appreciable decrement from baseline temperature (Table 2). No treatment failures occurred with either dose of ibuprofen.

A plot of mean temperatures over time (Figure) illustrates the comparative antipyretic effect of the four treatments. Patients receiving placebo exhibited no antipyretic response; mean temperature actually increased during the observation period. In contrast, the three active treatments exerted a significant antipyretic effect. Acetaminophen produced significant antipyresis compared with placebo at hours 3 through 5. Both doses of ibu-

Table 3.—AUC for Percentage Change in Temperature*

Treatment Group	Median AUC (≥95% Confidence Interval)
Ibuprofen, 7.5 mg/kg (n=12)	730 (576-839)
Ibuprofen, 10 mg/kg (n=8)	590 (160-875)
Acetaminophen, 10 mg/kg (n=8)	328 (−356-686)†
Placebo (n=9)	−67 (−629-120)‡

*AUC indicates area under the curve.
†$P=.05$ compared with ibuprofen therapy.
‡$P<.01$ compared with all active treatments.

profen provided significant antipyresis compared with placebo at hours 1 through 6. Antipyresis was significantly greater with 7.5-mg/kg ibuprofen therapy than with acetaminophen at hours 3 through 5. Ibuprofen produced a significant temperature decrement earlier after the dose, achieved greater maximum decrease in temperature, and provided longer duration of antipyresis than acetaminophen when the two drugs were administered in equivalent doses. No significant difference was detected in mean temperatures of patients receiving 7.5-mg/kg ibuprofen therapy vs patients receiving 10-mg/kg ibuprofen therapy any time after dosing.

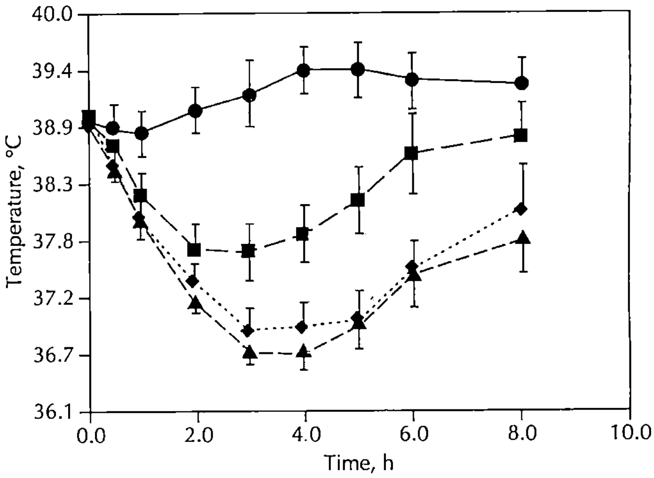
The difference in antipyretic effect between ibuprofen and acetaminophen is also evident in the AUCs of the four treatment groups for percentage change in temperature from baseline over time (Table 3). The median AUC of patients receiving acetaminophen was approximately 50% that of patients receving ibuprofen, reflecting the greater maximum antipyresis and longer duration of effect of ibuprofen.

No adverse reactions, abnormal physical findings, or abnormal laboratory results attributable to either ibuprofen or acetaminophen were observed.

COMMENT

Ibuprofen clearly provides a greater antipyretic effect than acetaminophen on a milligram-per-milligram basis. This includes both greater temperature decrement and longer duration of effect. There is no evidence that factors other than differences in effects of the two drugs contributed to the observed differences in antipyresis. Walson and associates[10] also found that 10-mg/kg ibuprofen therapy produced greater antipyresis than 10-mg/kg acetaminophen therapy, whereas antipyresis with 5-mg/kg ibuprofen therapy was similar to that of 10-mg/kg acetaminophen therapy. Although Walson et al[10] observed a difference in antipyretic effect between 5-mg/kg ibuprofen therapy and 10-mg/kg ibuprofen therapy, with the relatively small sample sizes in our study, we could not detect a difference in effect between 7.5-mg/kg and 10-mg/kg doses.

The longer duration of antipyresis with ibuprofen is not related to a longer elimination half-life of ibuprofen relative to acetaminophen because both have mean elimination half-lives of 1.0 to 2.0 hours in children with normal renal and hepatic function.[10,11] However, the longer duration of ibuprofen effect may be related to differences in optimally effective concentrations of the two drugs.[10] The dose-response curve for acetaminophen likely is shifted to the right of the ibuprofen dose-response curve, and maximum antipyresis may not be achieved with acetaminophen doses of 10 mg/kg or less. Acetaminophen exhibits a dose-response effect in doses exceeding 10 mg/kg.[12] Acetaminophen doses of 15 to 20 mg/kg might produce antipyresis equivalent to 10-mg/kg ibuprofen therapy, but that remains to be substantiated.



Comparison of mean patient temperatures over time among treatment groups 8 hours after administration of placebo, ibuprofen, or acetaminophen. Each point represents the mean temperature of patients in each treatment group at each measurement time. Bars represent ±SEM. No significant difference between the ibuprofen treatment groups was detected at any time. Mean temperatures in the ibuprofen groups were significantly lower than in the placebo group (circles) during hours 1 through 6. Mean temperatures in the acetaminophen group (squares) were significantly lower than in the placebo group at hours 3 through 5. Mean temperatures were lower in the group receiving 7.5-mg/kg ibuprofen therapy (triangles) than in the acetaminophen group at hours 3 through 5. Diamonds represent the group receiving 10-mg/kg ibuprofen therapy.

No adverse effects attributable to a single dose of either acetaminophen or ibuprofen were identified in this study. Several other single-dose studies[2-7,10] and two multidose studies[8,9] of ibuprofen administered to treat fever in children also have reported absence of adverse side effects. In a multicenter, long-term evaluation of the safety of ibuprofen,[13] 46 children with juvenile rheumatoid arthritis received 40 mg/kg per day for an average of 8 months; adverse side effects attributable to ibuprofen were limited to gastritis in one child. These results concerning side effects, although reassuring, do not rule out the possibility of rare adverse effects or risk of adverse effects in the presence of certain associated clinical conditions. A case of reversible renal failure in a volume-depleted child receiving ibuprofen has been reported.[14] Ibuprofen should be avoided in patients with dehydration or volume contraction because of the increased risk of ibuprofen-induced reduction of renal blood flow.[15]

Because of its familiarity, relative safety, and ready availability over the counter, acetaminophen will likely remain the most commonly used antipyretic in the foreseeable future. However, ibuprofen is a potent antipyretic and safe alternative for the selected febrile child who may benefit from antipyretic medication and who either cannot take acetaminophen or does not achieve satisfactory antipyresis with acetaminophen.

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Comparison of Multidose Ibuprofen and Acetaminophen Therapy in Febrile Children

Philip D. Walson, MD; Gary Galletta, PharmD; Fred Chomilo, PharmD; Nancy Jo Braden, MD; Laura Alexander Sawyer; Monte L. Scheinbaum, MD, PhD

• *Objective.*—To determine whether febrile children receiving 2.5-, 5-, or 10-mg/kg ibuprofen therapy via a liquid or 15-mg/kg acetaminophen therapy via an elixir every 6 hours for 24 to 48 hours show equivalent fever reduction or suffer adverse effects of the drug administered.

***Design.*—Randomized, double-blind, multidose, parallel-group, variable-duration (24 to 48 hours) clinical trial.**

***Setting.*—The academically affiliated Children's Hospital in Columbus, Ohio.**

***Participants.*—64 febrile (defined as oral or rectal temperature of 39°C to 40.5°C) but otherwise healthy children aged 6 months to 11 years 7 months randomly assigned to one of the four drug regimens.**

***Interventions.*—Treatment with either ibuprofen or acetaminophen as described above. Administration of antibiotics or intravenous fluids was allowed only after at least 24 hours of treatment with the assigned drug.**

***Measurements/Main Results.*—In 61 of the 64 evaluable patients, treatments were effective and well tolerated during the entire study. While the rates of temperature reduction and maximal reduction of fever after administration of the initial dose were equal for patients receiving 10-mg/kg ibuprofen therapy and 15-mg/kg acetaminophen therapy, and both regimens were more effective than smaller doses of ibuprofen in reducing fever, after the second dose (and continuing to the end of the study) there were no statistically significant differences in temperature response among the treatment groups. Six children were withdrawn from the study, two because of dosing errors, three because of hypothermia (temperature of less than 35.6°C; all three patients were in the acetaminophen group), and one because of gastrointestinal distress (this child was in the group receiving 2.5-mg/kg ibuprofen therapy). No other significant symptoms or adverse laboratory or physical findings were noted. While further confirmatory studies are needed, ibuprofen liquid (10 mg/kg) and acetaminophen elixir (15 mg/kg) administered every 6 hours for 24 to 48 hours appeared to be most effective in reducing fever. These two regimens were equally effective and equally tolerated in febrile children. Lower ibuprofen doses (2.5 and 5 mg/kg) were less effective than acetaminophen and 10-mg/kg ibuprofen therapy after the initial dose but were at least equally effective as these two higher-dose regimens thereafter.**

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The use of antipyretic medications for the symptomatic treatment of fever in children is still controversial.[1] However, antipyretic medications are commonly used both with and without physician approval. Aspirin, for many years the standard treatment for fever, has been replaced by acetaminophen largely because of concerns about related development of Reye's syndrome[2-4] and the dangers of overdoses.[5,6] However, the recent availability of nonprescription and prescription ibuprofen as well as concerns about the safety of acetaminophen[6-9] have resulted in the increased use of ibuprofen.[10]

Ibuprofen is a widely used, nonsalicylate, nonsteroidal, anti-inflammatory drug with marked analgesic,[11] anti-inflammatory,[12] and antipyretic effects.[13-23] In the United States, nonprescription tablet preparations of ibuprofen were approved in 1984 for antipyretic use in adults and children older than age 12 years. Ibuprofen liquids and tablets are now approved for prescription use in younger children.[10]

See also p 622.

While ibuprofen may have significant toxic effects to the kidneys in patients with renal disease as well as toxic effects such as allergic reactions, worsening of asthma, and gastrointestinal bleeding (as can all nonsteroidal, anti-inflammatory drugs), the drug is safe for the vast majority of patients. Even after extreme overdoses, most patients survive with only supportive care.[24] Many studies of single-dose ibuprofen therapy in febrile children

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have demonstrated antipyretic efficacy without serious toxicity.[13-17,22] Until recently in the United States, the antipyretic use of ibuprofen in young children has been limited by both the lack of suitable liquid formulations and limited data on efficacy and safety in children who received repeated doses. Use may increase now that liquid ibuprofen preparations have been approved.[10] Comparisons of multidose ibuprofen therapy with acetaminophen are scarce,[18-20] and many of the single-dose studies about which literature is available have compared recommended doses of ibuprofen with acetaminophen administered in doses that are lower than commonly accepted as effective.[25,26] Because of these facts, a study was undertaken to compare the antipyretic efficacy, safety, and patient acceptance of 24 to 48 hours of repeated dosing with an ibuprofen suspension (2.5, 5, or 10 mg/kg) with that of acetaminophen elixir (15 mg/kg; Tylenol, McNeil Consumer Products Co, Fort Washington, Pa) in febrile children.[27]

PATIENTS AND METHODS

A double-blind, double-dummy, block-randomized, multidose, parallel-group study design was used. Patients (aged 6 months to 11 years 7 months) weighing 6.8 to 56.1 kg who had been febrile for less than 48 hours and who had initial body temperatures (oral or rectal) of 39.0°C to 40.5°C were recruited. After obtaining written parental consent, patients were assigned to treatment groups and hospitalized for up to 48 hours for treatment with either ibuprofen or acetaminophen (Tylenol). Use of placebo control was believed to be ethically unjustifiable for a multidose study. The study was approved by the Institutional Review Board (Human Subjects Committee) of Children's Hospital, Columbus, Ohio.

Every 6 hours, each patient received two liquids, one of which contained placebo and one of which contained an active drug. The active drug was either ibuprofen (2.5, 5, or 10 mg/kg administered in liquid concentrations of 25, 50, or 100 mg/5 mL, respectively) or acetaminophen (15 mg/kg administered in an elixir of 160 mg/5 mL). Drugs and placebo liquids that matched the drugs in appearance were supplied by Boots Pharmaceuticals, Shreveport, La.

Patients were excluded if they had either taken any temperature-altering drug within 6 hours before the study or required antibiotic treatment from 12 hours before the initial dose of study medication to 24 hours after the first dose. Only patients who had previously taken acetaminophen or aspirin without serious adverse effects were accepted. Patients with significant gastrointestinal, renal, hepatic, cardiac, hematologic, bronchospastic, malignant, or central nervous system diseases (including seizure disorders); patients with vomiting, severe diarrhea, dehydration; and patients who had received investigational drugs within 1 month of the beginning of the study were also excluded.

Hematologic evaluations, blood chemistry tests, urinalysis, physical examination, and recording of temperature and other vital signs were performed before and after the study. Poststudy laboratory values were obtained at the last observation time point, which varied from 24 to 48 hours after the initial dose.

Both before and during the 24 to 48 hours after initial dosing, patients were monitored at intervals by study personnel. Two temperatures (oral or rectal, consistent for each patient) were obtained hourly for the first 6 hours, every 3 hours for the next 30 hours, and every 6 hours for the final 12 hours. Other vital signs (blood pressure, pulse, and respiratory rate) were monitored every 6 hours. Fluid intake, urine output, and adverse experiences were recorded with every temperature evaluation. Temperatures were obtained until the two highest temperatures were within 0.1°C of each other using an electronic temperature probe (model 811A, IVAC Corp, San Diego, Calif) with the timer disabled. End temperature was recorded when it remained stable for 30 seconds.

Patients who vomited the first dose of medication were observed and then allowed to reenroll more than 6 hours later if they still met all protocol criteria. Patients who became afebrile during the trial were to discontinue assigned study treatment as early as 27 hours after the initial dose if their temperatures were less than 37.2°C both 24 and 27 hours after starting treatment.

Patients were withdrawn early from the study if (*a*) temperature either increased to above 40.5°C or decreased to below 35.6°C; (*b*) antibiotic treatment or intravenous fluids were required during the initial 24 hours of the study; (*c*) any severe adverse physical events occurred; or (*d*) patients, their parents, or their guardians withdrew consent.

Patients were allowed to ingest only up to 180 mL of room-temperature water with the first dose, after which no liquids were permitted for 1 hour. After the first hour, patients were allowed up to 180 mL of fluid every 2 hours and food ad libitum.

STATISTICAL METHODS

The sex and race of patients in the four treatment groups were compared using a χ^2 statistic derived from the FREQ procedure of the SAS statistical software package.

Descriptive statistics (numbers and mean values ±SD of the continuous demographic parameters [age, height, weight, and baseline temperature]) for all patients in each treatment group were tested for normality using the Kolmogorov D statistic in the SAS univariate procedure, with significance defined at $P \leq .01$. If the distribution was normal, a single-factor analysis of variance (ANOVA), with treatment group as the factor, was performed with ANOVA on ranks (using the NPAR1WAY procedure of the SAS statistical software package). Results of ANOVA were examined for significant treatment effects ($P \leq .05$); when such an effect was present, comparisons of treatment were made using repeated *t* tests, with significance set at $P < .05$. If the parameter distribution was not normal, the treatment effect was evaluated using the Kruskal-Wallis test in the SAS NPAR1WAY procedure.

The primary measure of antipyretic efficacy was the patients' temperatures over time. From these measurements, the following parameters were calculated: (1) change in temperature from baseline; (2) area under the curve (AUC) with respect to time (temperature change per hour); (3) percentage reduction of fever per hour; (4) AUC of percentage reduction of fever per hour; (5) maximal reduction of fever (R_{max}) for the first dose; and (6) time to maximal reduction of fever (T_{max}, hours) for the first dose.

Percentage reduction of fever was calculated as the change in temperature from baseline divided by the difference between normal temperature (37°C) and baseline temperature. Areas under the curve were calculated for hours 0 through 6, 0 through 12, 0 through 24, and 0 through 48 using the trapezoidal rule. When temperatures decreased to below 37° C, the resulting percentage reduction exceeded 100%.

The number of patients withdrawn before scheduled completion of the study was tabulated. Such patients were to be monitored for at least 9 hours after administration of the last dose of study medication. For these patients, only temperature measurements obtained before and including those 9 hours were used in the efficacy analysis; all other temperature measurements were excluded from the analyses. If withdrawal occurred after the 30- or 36-hour dose, only temperature measurements made within the next 12 hours (ie, up to 42 and 48 hours, respectively) were used for efficacy analysis because temperature was not measured 9 hours after the last dose (ie, at 39 and 45 hours, respectively).

All efficacy parameters except T_{max} were analyzed with parametric ANOVA (using the GLM procedure of the SAS statistical software package), with treatment being the only factor in the model. When the overall *F* statistic was significant ($P \leq .05$) or nearly so ($P < .10$), individual pairwise treatment comparisons were made using repeated *t* tests, with significance defined at $P \leq .05$. The appropriateness of the model was evaluated using a test of normality on the residuals (SAS univariate procedure).

Table 1.—Demographics of Patients Included in Efficacy Analysis*

Treatment	Age, y	Height, cm	Weight, kg	Baseline Temperature, °C	M/F	Race, White/Black/Asian
Ibuprofen						
2.5 mg/kg (n=15)†	6.1±2.6	113.2±17.0	21.7±11.1	39.4±0.4	8/7	8/7/0
5.0 mg/kg (n=15)	5.8±2.8	114.4±19.4	21.3±6.4	39.4±0.3	6/9	10/5/0
10.0 mg/kg (n=15)	4.9±3.1	107.2±211.7	20.1±11.3	39.4±0.4	9/6	5/10/0
Acetaminophen						
15.0 mg/kg (n=16)†	5.2±3.0	110.4±21.3	20.8±10.7	39.3±0.3	7/9	9/6/1
Total (N=61)	5.5±2.9	111.3±19.7	21.0±9.8	39.4±0.3	**30/31**	**32/28/1**

*Values for columns two through five are means±SDs.
†Height was not recorded for one child in this group.

The T_{max} was treated as a discrete parameter because of the limited number of possible responses. Consequently, it was analyzed using the Kruskal-Wallis test in the SAS NPAR1WAY procedure.

Efficacy analyses were performed with both "observed" and "endpoint" data of AUC and percentage reduction of fever. When observed data were used, a value was considered missing for a specific parameter if any information was missing (eg, if patients dropped out early). For endpoint analysis, the last valid observation was used in place of missing data.

Patient responses to treatment were evaluated before researchers were informed of which patients were assigned to each treatment group. Safety analyses were based on these evaluations of adverse experiences, vital signs, results of physical examination, and results of clinical laboratory tests. Any change in a vital sign value that exceeded 25% of the baseline value was noted.

Adverse experiences were evaluated in relation to individual treatment groups and to all ibuprofen groups as a whole. The number of patients reporting an adverse effect, the number of adverse effects per patient, the degree of severity of the adverse effects, and the body system involved were examined. Differences between treatment groups in incidence of adverse effects for each body system were evaluated using a χ^2 test.

For results of clinical laboratory tests performed before and after the assigned period of drug administration, descriptive statistics were used to evaluate shifts in each treatment group. For each treatment group, a separate tabulation was performed showing the incidence of shifts from clinically nonsignificant values before the study to clinically significant values at the end of the study.

RESULTS

Demographic Characteristics of Patients

Sixty-four patients were enrolled in the study. Three of these 64 were entered into the study a second time, one after vomiting the first dose and two after a timing error in their dosing schedules. Each of the 64 patients was included in the safety evaluation, but three were excluded from the efficacy analysis—two who vomited the initial dose and did not receive additional doses and one who inadvertently received 1.7 times the scheduled dose.

The 61 patients included in the efficacy analysis are described in Table 1. Patients ranged in age from 6 months to 11 years 7 months and weighed between 6.8 kg and 56.1 kg. Height ranged from 67.0 cm to 158.0 cm. Baseline (0-hour) temperatures ranged from 39°C to 40.1°C, except for one patient who was medicated when his baseline temperature reached 40.6°C during the initial evaluation period. These mean values were not altered by excluding the three patients not included in the efficacy analysis.

Eleven of the 61 patients had been participants in an earlier 8-hour study of single-dose ibuprofen therapy (5 or 10 mg/kg) compared with single-dose acetaminophen therapy (10 mg/kg) in the treatment of pyrexia.[22] In the present study, four of these patients were assigned to the group receiving 2.5-mg/kg ibuprofen therapy; three, to the group receiving 5-mg/kg ibuprofen therapy; two, in the group receiving 10-mg/kg ibuprofen therapy; and two, in the group receiving acetaminophen.

No differences were found between the four treatment groups in demographic parameters or baseline temperatures (Kruskal-Wallis test, SAS NPAR1WAY procedure).

All patients had an infectious illness, in most cases, viral pharyngitis. Five patients had concurrent secondary diagnoses on study entry—one had tinea; one, accidental perineal trauma; and three, allergic rhinitis.

No patient used an antibiotic earlier than 24 hours after the initial dose of study medication. Thirteen patients, distributed evenly among the treatment groups (two to four each), received an antibiotic more than 24 hours after initial dosing. Twelve received either penicillin V potassium (n=7) or amoxicillin (n=6). These 13 patients constituted too small a group to warrant a separate efficacy analysis.

Three patients received a concomitant medication other than an antibiotic during the 48-hour study period. Two (both in the group receiving 10-mg/kg ibuprofen therapy) were included in the efficacy analysis. One received three applications of clotrimazole cream to treat tinea. The other received a single application of 1% phenylephrine hydrochloride nose drops to treat allergic rhinitis. The third was excluded from the efficacy analysis because he received acetaminophen (chewable Tylenol) to treat fever after he vomited his first dose of study medication (5 mg of ibuprofen per kilogram).

One patient was incorrectly administered 1.7 times the scheduled amount of study drug (4.3 vs 2.5 mg of ibuprofen per kilogram) because her weight was misread. Three patients missed one dose of study medication owing to nursing errors; one did not receive the 18-hour dose; one accidentally missed the 6-hour dose (but was subsequently withdrawn from the study because she was afebrile at hour 27); and one inadvertently missed the required 42-hour dose but was evaluated through hour 48. One patient received the fourth (and last) dose 3 hours early (at 15 hours rather than 18 hours after baseline) and was afebrile at hour 24. Only data obtained before dosing errors occurred were included in the efficacy analysis.

Six patients included in the efficacy analysis were pre-

Table 2.—Treatment and Study Experience of Patients in the Efficacy Analysis*

Condition for Study Exit	Ibuprofen 2.5 mg/kg	Ibuprofen 5 mg/kg	Ibuprofen 10 mg/kg	Acetaminophen, 15 mg/kg	Total
Completed 48 hours of treatment	4	3	3	6	**16**
Afebrile patient withdrawn per protocol	10	11	11	7	**39**
Withdrawn because of adverse experience	1	0	0	3	**4**
Withdrawn (other)	0	1	1	0	**2**
Total	**15**	**15**	**15**	**16**	**61**

*Values are numbers of patients.

maturely withdrawn from the study for reasons other than becoming afebrile during the trial. Four were withdrawn because of adverse effects of treatment, and two patients were withdrawn because of errors in dose administration (Table 2).

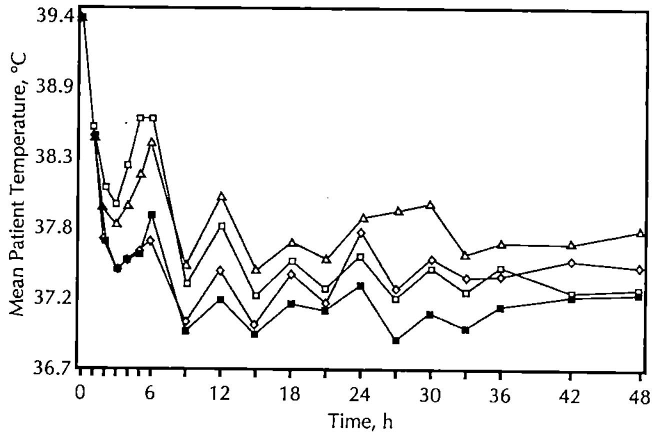
Most patients (39 of 61) included in the efficacy analyses were withdrawn before completion of 48 hours of treatment because of resolution of fever (Table 3), including three patients (one in each ibuprofen group) who were withdrawn after an afebrile temperature was recorded at only one of the evaluation times rather than the two required according to protocol. We decided that this was not sufficient cause to exclude these two patients from the efficacy analysis. Only 16 patients required treatment for the entire 48 hours (Table 3).

Efficacy

All temperature data were ultimately subjected to endpoint analysis. No temperature measurements were missing for any patient through the first 12 hours, so the results of observed and endpoint analyses for this period were identical. The small number of patients failing to complete the 24-hour evaluation (five of 61) was not believed to affect the observed results of analysis; endpoint analysis was automatically required for the 48-hour evaluation because it was permissible to withdraw patients after the 27-hour evaluation.

A plot of mean temperature by treatment group at each evaluation interval is presented in the Figure. By 6 hours after initiation of drug therapy, the mean temperature decreases for ibuprofen administered in doses of 2.5 mg/kg and 5 mg/kg were less prominent than for both ibuprofen administered in doses of 10 mg/kg and acetaminophen. These differences were less obvious in the 12-hour measurements.

Analysis of the mean percentage reduction of fever at selected intervals showed a significant ($P \leq .05$) treatment effect only at 0 through 6 hours (Table 4), when 10-mg/kg ibuprofen therapy and acetaminophen appeared to lower temperature more than either of the smaller doses of ibuprofen. Only data from the group receiving 2.5-mg/kg ibuprofen therapy had a significantly smaller AUC for percentage reduction of fever (indicating less effectiveness) than the group receiving either 10-mg/kg ibuprofen therapy or acetaminophen. Differences among the treatment groups at the 12-hour, 24-hour, and 48-hour evaluations were significant only in the AUC of mean percentage reduction of fever. For hours 0 through 12 and 0 through 24, this AUC for 5-mg/kg ibuprofen therapy was lower than the corresponding AUC for acetaminophen therapy. There were no statistically significant differences between 10-mg/kg ibuprofen therapy and acetaminophen at any interval.



Mean temperatures plotted over time for each of the four treatment groups. Open squares indicate 2.5-mg/kg ibuprofen therapy; triangles, 5-mg/kg ibuprofen therapy; diamonds, 10-mg/kg ibuprofen therapy; and closed squares, 15-mg/kg acetaminophen therapy.

Analysis of variance of the R_{max} during the first dosing interval showed a significant overall treatment effect ($P = .04$). Multiple pairwise comparisons showed the mean percentage reduction of fever in the group receiving 2.5-mg/kg ibuprofen therapy (72.9%) to be significantly less than for either the group receiving acetaminophen (94.2%) or the group receiving 10-mg/kg ibuprofen therapy (96.5%) (Figure). In addition, the mean percentage reduction of fever for the group receiving 5-mg/kg ibuprofen therapy (76.0%) was significantly lower than that of the group receiving 10-mg/kg ibuprofen therapy. Results of no other pairwise comparisons were statistically significant.

Results of the Kruskal-Wallis test for the T_{max} (Figure) during the first dosing interval also showed a significant overall treatment effect ($P = .05$). Results of multiple pairwise comparisons showed the mean T_{max} in the group receiving 2.5-mg/kg ibuprofen therapy (2.9 hours) to have occurred sooner than that for either the group receiving 10-mg/kg ibuprofen therapy or the group receiving acetaminophen (mean for both groups, 4.1 hours). Results of no other pairwise comparisons were statistically significant.

Safety and Tolerance

For all 48 patients receiving ibuprofen (including the three patients excluded from the efficacy evaluation), the greatest number of patients (40) reported adverse experiences related to the respiratory system, followed by headache (23 patients) and gastrointestinal effects (18 pa-

Table 3.—Number of Patients in Each Treatment Group at Each Evaluation Interval

Evaluation Interval, h	Ibuprofen 2.5 mg/kg	Ibuprofen 5.0 mg/kg	Ibuprofen 10 mg/kg	Acetaminophen, 15 mg/kg	Total
0	15	15	15	16	61
1	15	15	15	16	61
2	15	15	15	16	61
3	15	15	15	16	61
4	15	15	15	16	61
5	15	15	15	16	61
6	15	15	15	16	61
9	15	15	15	16	61
12	15	15	15	16	61
15	15	15	15	16	61
18	15	15	15	14	59
21	15	15	15	14	59
24	15	14	14	13	56
27	15	14	14	13	56
30	8	7	9	8	32
33	8	7	9	8	32
36	5	6	6	6	23
42	4	6	6	6	22
48	4	3	3	6	16

tients). Respiratory-related effects were also the most commonly reported adverse effect among the 16 patients receiving acetaminophen (12 patients), followed by headache (seven patients). For all groups, most of the reported adverse experiences were related to the febrile illness rather than to the treatment.

When adverse experiences occurring before the study and those considered to be only remotely related to the study treatments were excluded from analysis, the percentage of patients reporting adverse experiences decreased sharply. For all ibuprofen groups combined, sweating was the most common complaint (eight patients), followed by gastrointestinal effects (seven patients). For the acetaminophen group, the most common adverse experiences were hypothermia, abdominal pain, and agitation and/or nervousness, with three patients (19%) reporting each of these effects.

There were no significant differences between treatment groups in the number of patients who reported at least one adverse effect to any particular body system. Some adverse effects were judged to be either possibly or probably drug related. Posttreatment reports of one or more such effects to any particular body system were too few to permit statistical comparison of the treatment groups.

No adverse effects of greater than moderate severity were reported. Of the 141 reported adverse experiences after treatment with ibuprofen, 124 (88%) were mild, whereas all reported adverse experiences (48) in the acetaminophen group were mild.

Only four patients experienced adverse effects that resulted in withdrawal from the study. One patient receiving 2.5-mg/kg ibuprofen therapy was withdrawn after complaints of moderate nausea, vomiting, and abdominal pain, which might have been drug-related. The other three patients, each of whom received acetaminophen, were withdrawn because of hypothermia occurring after administration of two to three doses. We believe the hypothermia in all three cases was probably drug-related.

Neither vital signs nor results of physical examinations revealed significant changes not directly related to the diseases treated. Except for percentage of neutrophils and aspartate aminotransferase levels, mean values obtained with hematologic testing, blood chemistry analysis, and urinalysis were not significantly different among the treatment groups. Except for one patient who experienced clinically significant decreases in both hemoglobin (19-g/L decrease) and hematocrit (0.064 decrease) levels after treatment with ibuprofen (2.5 mg/kg), none of these changes were judged to be clinically relevant. Differential cell count showed a significantly ($P<.05$) greater decrease in neutrophils in the group receiving 2.5-mg/kg ibuprofen therapy (0.28 decrease) compared with the group receiving 5-mg/kg ibuprofen therapy (0.16 decrease) and the group receiving acetaminophen (0.16 decrease). The decrease in the group receiving 10-mg/kg ibuprofen therapy (0.23) was similar to that in the group receiving 2.5-mg/kg ibuprofen therapy.

Posttreatment aspartate aminotransferase values in the group receiving 5-mg/kg ibuprofen therapy had significantly decreased (5.5-U/L decrease from baseline) compared with posttreatment values in the group receiving 10-mg/kg ibuprofen therapy (5.2-U/L increase from baseline). This change in aspartate aminotransferase levels in the group receiving 5-mg/kg ibuprofen therapy was not so large when compared with the changes in the groups receiving 2.5-mg/kg ibuprofen therapy (0.1-U/L decrease) or acetaminophen (2.5-U/L decrease).

Table 4.—Fever Reduction and Length of Treatment*

Treatment	0-6 h Mean % Decrease in Temperature	0-6 h AUC	0-12 h Mean % Decrease in Temperature	0-12 h AUC	0-24 h Mean % Decrease in Temperature	0-24 h AUC	0-48 h Mean % Decrease in Temperature	0-48 h AUC
Ibuprofen								
2.5 mg/kg	34.5	261†	73.1	696	79.6	1721	88.6	3810
5 mg/kg	38.9	297	58.2	689‡	62.9	1572‡	70.5	3286
10 mg/kg	73.2§	385	84.0	929	67.8	1995	80.0	3933
Acetaminophen, 15 mg/kg	65.9	377	94.3	938	87.5	2100	89.4	4400
F	2.73	3.24	1.50	2.60	1.02	2.43	0.67	1.98
P	.05	.03	.22	.06	.39	.07	.58	.13

*AUC indicates area under the curve.
†$P<.05$ compared with acetaminophen and 10-mg/kg ibuprofen therapy.
‡$P<.05$ compared with acetaminophen.
§$P<.05$ compared with 2.5-mg/kg and 5.0-mg/kg ibuprofen therapy.

In the group receiving 2.5-mg/kg ibuprofen therapy, five patients had posttreatment neutrophil counts of less than 1.25×10^9/L, one of whom also had mild leukopenia (white blood cell count, less than 3.5×10^9/L). Except for the group receiving 2.5-mg/kg ibuprofen therapy, one patient in each group had decreased neutrophil counts. One patient in the group receiving 10-mg/kg ibuprofen therapy had pretreatment neutropenia but demonstrated a posttreatment decrease in neutrophils of more than 20%. All patients were asymptomatic by 2 to 4 weeks after treatment.

There were no significant or unexpected changes in either urea nitrogen or creatinine levels in any group. In fact, posttreatment values of creatinine in serum decreased in all groups, and the posttreatment values of urea nitrogen in blood decreased in all groups except the group receiving 2.5-mg/kg ibuprofen therapy. In this group, the increase was insignificant (from a mean baseline value of 3.8 mmol/L to a posttreatment mean of 4.0 mmol/L).

One patient receiving ibuprofen (2.5 mg/kg) had an increased alanine aminotransferase level after treatment (from 8 U/L at baseline to 71 U/L). During the same period, the patient's aspartate aminotransferase level decreased. One patient receiving ibuprofen (10 mg/kg) had an increased alanine aminotransferase level (from 23 U/L at baseline to 112 U/L after treatment) coupled with an increased aspartate aminotransferase level (from 57 U/L at baseline to 133 U/L after treatment), but this patient's prestudy aspartate aminotransferase level had been above normal. No clinically significant, abnormally elevated alkaline phosphatase or total bilirubin levels were reported in any patients.

None of the results of hematologic tests, urinalysis, or blood chemistry tests were thought to have been affected by the study medications.

COMMENT

The antipyretic efficacy of both ibuprofen and acetaminophen was confirmed by analyses of temperature changes, AUC for change in temperature with respect to time, percentage reduction of fever, AUC for percentage reduction of fever with respect to time, R_{max}, and T_{max}.

When administered every 6 hours, there were no significant differences between 10-mg/kg ibuprofen therapy and 15-mg/kg acetaminophen therapy for any of these parameters. A previous single-dose, 8-hour study[22] demonstrated antipyretic advantages for 10-mg/kg ibuprofen therapy compared with 10-mg/kg acetaminophen therapy. The lack of difference in treatment effect between these two therapies in this multidose study could be related to the use of a higher acetaminophen dose than in the previous study (15 mg/kg vs 10 mg/kg)[25] or a different administration interval (every 6 hours vs every 8 hours). Of note, Wilson et al[28] used computer simulations to predict that acetaminophen doses of 13.3 mg/kg administered every 4 hours except while asleep (66.5 mg/kg per day) would produce maximally effective fever reduction. This is similar to the total daily dose (60 mg/kg) used in this study.

While a plot of change in temperature over time (Figure) appeared to show that mean temperature initially decreased more in patients treated with either 10-mg/kg ibuprofen therapy or acetaminophen than in patients treated with the smaller doses of ibuprofen (2.5 mg/kg or 5 mg/kg), the differences were statistically significant only for the lowest dose of ibuprofen (2.5 mg/kg) and only for the first dose. Thereafter, no statistically significant differences were found among any of the treatment groups.

Six hours after starting treatment, the percentage reduction of fever for the group receiving 10-mg/kg ibuprofen therapy was not statistically different from that of the acetaminophen group. The previously reported differences in the effectiveness of 10-mg/kg ibuprofen therapy compared with 10-mg/kg acetaminophen therapy 6 hours after initiating treatment[22] were not obvious when a higher acetaminophen dose (15 mg/kg) was used.

Although T_{max} for the first dose occurred significantly sooner with 2.5-mg/kg ibuprofen therapy than with 10-mg/kg ibuprofen therapy, this does not imply a clinical advantage for the lower dose because its antipyretic effect was weaker.

All treatments were generally well tolerated, and there were no significant differences in safety between the treatments based on the incidence and severity of adverse experiences; changes in vital signs (blood pressure, pulse, and respiratory rate) and results of physical examinations; and hematopoietic, renal, and hepatic functions. Clearly, tolerability in this small group cannot be used to predict safety in the general population, especially in patients with renal disease or patients receiving diuretics who might be more prone to toxic effects to the kidneys caused by ibuprofen. Gastrointestinal upset, which occurred more frequently in the ibuprofen groups than in the acetaminophen group, is more common with nonsteroidal, anti-inflammatory drugs than with acetaminophen. The significance of the hypothermia is unknown. All abnormally low temperatures were confirmed with multiple measurements of core (rectal) temperatures. Although there is no known association between acetaminophen and hypothermia, repeated high doses of acetaminophen may be responsible for such an effect. However, there were no lasting sequelae of hypothermia in our patients, and mild hypothermia has no known complications.

The decision to treat fever must be made case-by-case. If fever is treated, clinicians must appreciate that the temperature response cannot be used to rule out serious disease.[29] The choice of antipyretic, acetaminophen or ibuprofen, must also be made case-by-case and should take into account both the risks and benefits of the drug considered. However, in terms of efficacy, 10 mg of ibuprofen per kilogram administered every 6 hours appears comparable in antipyretic efficacy to 15 mg of acetaminophen per kilogram and perhaps more effective than lower doses of ibuprofen (2.5 and 5 mg/kg).

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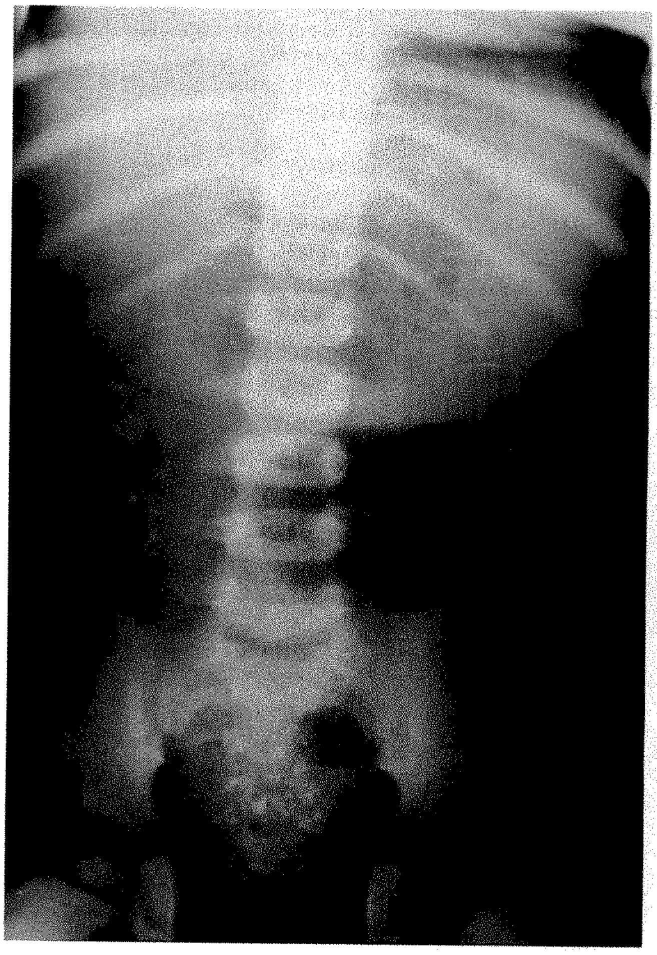
Radiological Case of the Month

Lutfi Jaber, MD; Michael Grunebaum, MD; Rina Zaizov, MD (Contributors); *Beverly P. Wood, MD* (Section Editor)

A 2-year-old Israeli girl was born after 30 weeks' gestation to parents of Ethiopian origin. She was referred to the hematology clinic because of longstanding anemia and was treated with parenteral iron. She underwent additional examination because of poor response to the treatment and poor compliance. The patient had no relevant family history.

Physical and psychomotor development were normal except for a wide base gait. Laboratory findings were as follows: white blood cell count, 8.3×10^9/L; hematocrit, 0.25; hemoglobin, 80 g/L; platelet count, 307×10^9/L; mean corpuscular volume, 55 fL; mean corpuscular hemoglobin, 17.5 pg; and mean corpuscular hemoglobin concentration, 318 g/L. Blood chemistry was normal except for an elevated alkaline phosphatase level of 350 U/L. Results of a hematologic workup revealed a low serum iron level of 2.5 µmol/L, total iron-binding capacity of 84 µmol/L, a low iron saturation level of 0.03, and a low ferritin level of 5 µg/L—all suggestive of severe iron deficiency anemia. Levels of glucose-6-phosphate dehydrogenase folic acid and vitamin B_{12} were within normal limits. An abdominal roentgenogram was obtained (Figure).



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Contributed from the Sambur Center for Pediatric Hematology/Oncology (Drs Jaber and Zaizov) and the Department of Pediatric Radiology (Dr Grunebaum), Beilinson Medical Center, Petah Tiqva, Israel, and the Sackler School of Medicine, Tel Aviv (Israel) University.

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The Editors welcome contributions to Pathological Case of the Month, Picture of the Month, *and* Radiological Case of the Month. *Those who wish to contribute should send their manuscripts to Dr Gilbert-Barness (*Pathological Case of the Month*), Center for Health Sciences, E5/326, University of Wisconsin Hospitals and Clinics, Madison, WI 53792; Dr Tunnessen (*Picture of the Month*), The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104; or Dr Wood (*Radiological Case of the Month*), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Denouement and Discussion

Pica

Pica is a name derived from the Latin word meaning magpie. It was defined as a perversion of appetite with persistent and purposeful ingestion of unsuitable nonnutritive substances.[1] Others defined it as ingesting or sucking of objects by children older than age 18 months[2] or eating of both food and nonfood substances.[3] It occurs worldwide at all ages and in all strata of society. The reported prevalence rate of pica in children aged 1 to 6 years varies from 10% to 32%.[4] Each local group seems to specialize in ingesting one particular substance.

The association of pica with iron deficiency anemia is well known. This dates at least from the 10th century when Avicenna[5] recommended "iron steeped in fine wine" as treatment.

Lanskowsky,[1] who studied the origin of pica in South African children, concluded that iron deficiency was a major cause and that iron therapy was curative. These results were supported by Coltman[6] and Crosby.[3]

The debate centers over whether pica causes the iron deficiency or is a consequence of the deficiency. The former is indicated by the possibility that ingestion could interfere with absorption of the deficient material. On the other hand, many isolated cases have been reported involving the compulsive ingestion of unusual substances such as cigarette ash, match heads, or ice, all of which were associated with iron deficiency and all of which were cured with iron supplementation therapy.

Pica does not represent a single disease, but is associated with a wide range of physical, environmental, social, and mental disturbances.[5] It is habitual or associated with personality disorders such as neuroses and psychoses and is the most frequent eating dysfunction in mentally handicapped patients.[5]

Pica cannot be explained by a single causative condition. Bonsdorff[7] related it to functional disorder in the hypothalamus, which is sensitive to changes in iron levels. This theory does not explain pica in children without nutritional disturbances or the curing of pica with zinc administration.[8] Certain types of pica were related to compulsive disorders or addiction. Some forms of pica, such as wood chewing for resultant good teeth and gums, are physiologic.[9] Stress in later life may cause reappearance of the habit.

The importance of pica is heightened when craving results in malnutrition and poisoning. The association of pica with lead poisoning is well known, but other serious complications have also been reported, such as resistant hypertension due to ingestion of baking soda; profound muscular weakness and hypokalemia due to clay ingestion; fecal impaction due to geophagia; pseudoporphyria due to paper eating; and parasite infestation.

Most cases of pica resolve within 1 week with iron administration.[1,3] Other cases not associated with iron deficiency may require multidisciplinary investigation and control.

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SPECIAL FEATURE

Radiological Case of the Month

Paul Govaert, MD; Jules Leroy, PhD; Jacques Caemaert, MD (Contributors); *Beverly P. Wood, MD* (Section Editor)

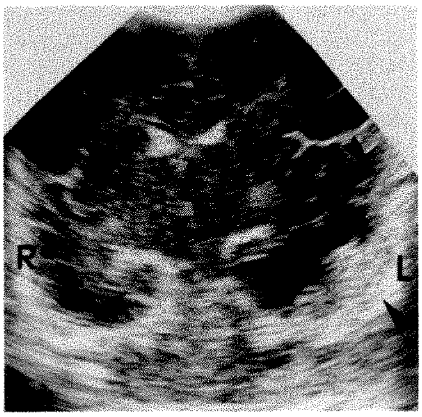
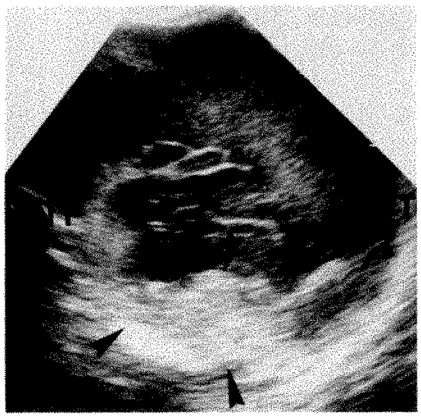


Figure 1.



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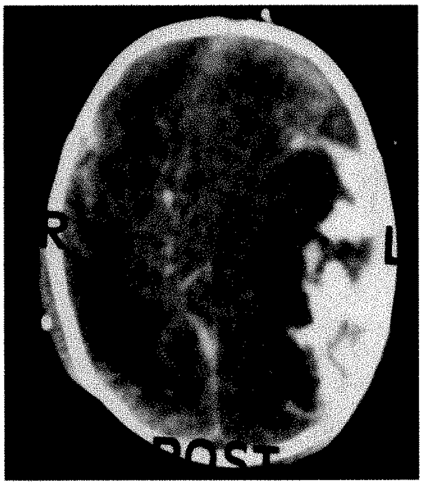

Figure 3.

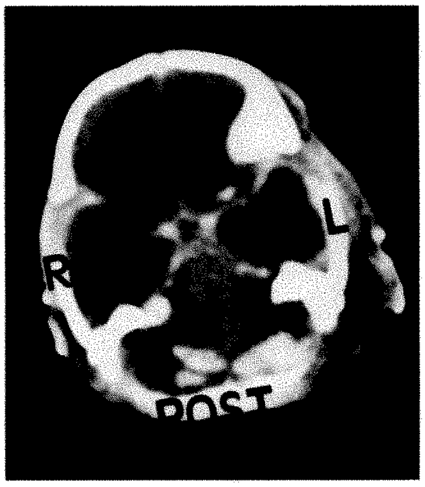

Figure 4.

A female infant was delivered spontaneously at 32 weeks' gestation after several weeks of amniotic fluid leak. The birth weight was 2100 g. The Apgar score was 9 at 1 and 5 minutes. Moderate respiratory distress was treated effectively with 10 hours of assisted ventilation. At age 10 days, an episode of bradycardia and apnea led to further investigation, which revealed leukopenia, thrombocytopenia (36×10^9/L), and a serum C-reactive protein level of 0.06 g/L. Results of a lumbar puncture were normal. Cefotaxime (50 mg/kg of body weight every 8 hours) and netromycine (3 mg/kg of body weight every 18 hours) therapy was begun for management of *Klebsiella pneumoniae*–related septicemia. Development of a profound metabolic acidosis required ventilatory support, and, because of hypotension, fresh frozen plasma, albumin, and vasopressors (dopamine, dobutamine, and naloxone) were administered. The infant became anemic (hemoglobin level, 90 g/L) and developed generalized seizures, jerky nystagmoid eye movements, and a mydriatic left pupil.

One day after identification of septicemia, cranial ultrasound and computed tomographic scans were performed (Figs 1 through 4), followed by an emergency craniotomy to manage an increasingly tense fontanelle and bradycardia. Continuous seizures occurred after surgery, and the patient died at age 40 days.

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Denouement and Discussion

Extensive Neonatal Subarachnoid Hematoma

Figs 1 and 2.—*Ultrasound scans (7.5 MHz) in coronal and left parasagittal planes showing a large extra-axial hyperechoic collection between the left temporal lobe and the skull (arrowheads). This hemorrhage is located beneath the insula of Reil and has irregular internal margins. A small amount of subependymal bleeding is present near the right caudate nucleus.*

Figs 3 and 4.—*Noncontrasted computed tomographic scan (supratentorial and infratentorial locations) confirms the presence of large extra-axial hemorrhage on the left, extending beneath the left temporal lobe and filling the cortical sulci. The hemorrhage exerts a mass effect, compressing the ipsilateral ventricle and displacing the midline at least 1 cm. Hemorrhage beneath the tentorium is present above the cerebellum and vermis and compresses the fourth ventricle. The basal cisterns are filled with blood.*

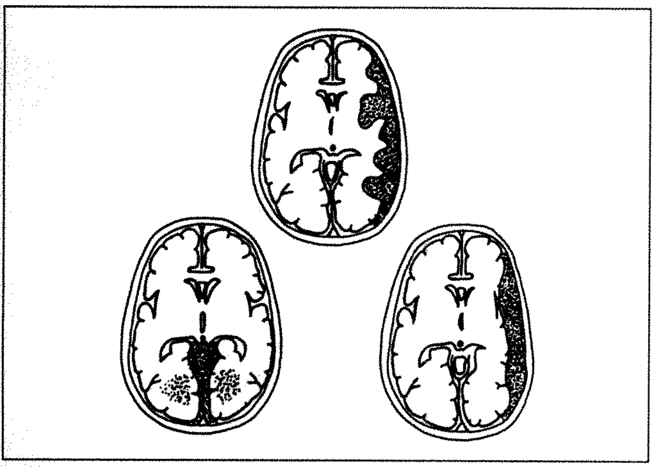

Fig 5.—*Schematic drawings (from left to right), of primary neonatal subarachnoid hemorrhage, subarachnoid hematoma, and subdural hematoma. Dots represent extravascular blood.*

During parietotemporal craniotomy of the left side of the brain, a large clot underlying the arachnoid membrane was revealed. The hemorrhage covered the insula and cortical sulci. In the absence of physical injury and with the backgound of hemostatic and hemodynamic instability, the hemorrhage on ultrasound and computed tomographic scanning was indicative of subarachnoid hematoma unrelated to germinal matrix hemorrhage of the premature infant. This patient died in status epilepticus secondary to generalized cerebral ischemia due to rapidly increased intracranial pressure and impaired focal perfusion.

Relatively small amounts of neonatal subarachnoid hemorrhage represent a common form of intracranial bleeding in the full-term or near full-term newborn.[1,2] Diagnosis using computed tomography has been reported and subsequently refined.[3] Two major etiologic categories are distinguished, one of which follows birth injury (eg, high and forceful vacuum extraction). Even in the absence of birth asphyxia, the presence of extravasated blood in the cerebral interhemispheric fissure and on the tentorium and superior cerebellar vermis may be a cause of grunting, hypotonia, fluctuating consciousness, irritability, opisthotonus, cyanotic spells, fixed bradycardia, unconjugated hyperbilirubinemia, and focal or generalized seizures.[2,3] Long-term sequelae are seizures and communicating hydrocephalus.[4,5]

The pathologic features of neonatal subarachnoid hematoma, such as those of the dramatic case presented here, are described by Larroche.[6] In these instances, the hemorrhage was located on one or more cerebral lobes and was unilateral. The clot, up to 2-cm thick in our patient, may damage the adjacent cortex and cause hemorrhagic cerebral necrosis. Its more frequent development on the left side of the cerebrum is unexplained.[6] The underlying cause of hemorrhage is failure of hemostasis.[6-8] Distinguishing subarachnoid hematoma from subdural hematoma is clinically impossible, but may be possible with the use of ultrasonography and computed tomography[9] (Fig 5). The presence of cerebral edema, necrosis, or uncal herniation indicates a very poor outlook.[10,11] This case adds supportive evidence to the view that extensive, deep, and compressing hematoma with extension into the cerebral fissures and sulci may increase the probability of subsequent cerebral damage and uncal herniation. Therefore, early recognition of the precise location and implications of intracranial bleeding is important in the management of neonates with hemostatic disorders.

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SPECIAL FEATURE

Picture of the Month

Elizabeth Secord, MD; Umit Emre, MD; Binita R. Shah, MD (Contributors);
Walter W. Tunnessen, Jr, MD (Section Editor)

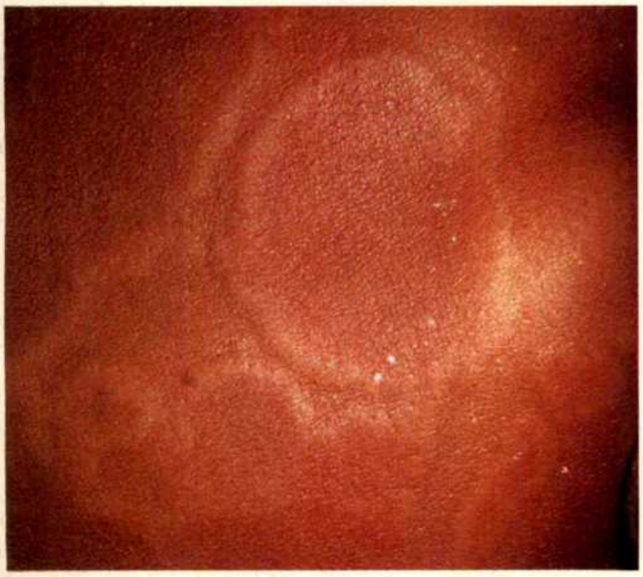
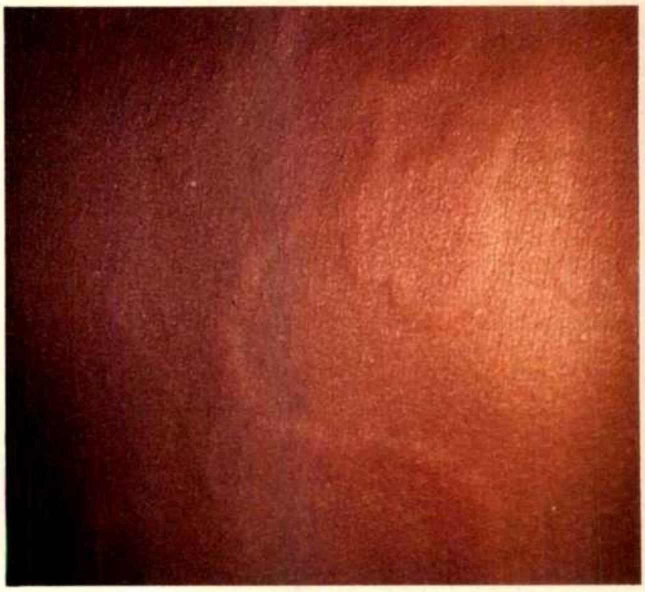


Figure 1.



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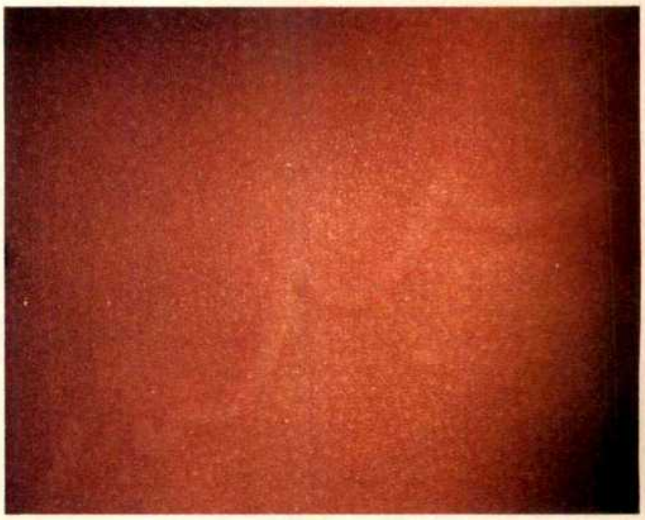

Figure 3.

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Contributed from The Children's Medical Center of Brooklyn (NY).

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Denouement and Discussion

Erythema Marginatum in Acute Rheumatic Fever

Figs 1 and 2.—*Annular plaques (complete rings) of varying sizes with macular centers and erythematous, raised margins. Note the serpiginous borders formed by coalescence of several partial rings.*

Fig 3.—*Polycyclic figure formed by coalescence of adjacent lesions.*

Historical Background

The polycyclic ringed lesions that eventually were called erythema marginatum (EM) were identified as being associated with acute rheumatic fever (ARF) by Bright in 1831.[1] Cheadle used the term *erythema marginatum* to identify the lesions associated with ARF in 1889, and Lehndorf and Leiner later called the same lesions "erythema annulare" in 1922.[2] The two names were used interchangeably until 1938, when Keil studied 523 cases of rheumatic fever at Mt Sinai Hospital, New York, NY, and described variants of a rash with a marginated border. The macular rash was labeled erythema marginatum, and the papular variant was referred to as erythema annulare.[3] Around the same time, Perry[4] monitored the appearance of skin eruptions in patients with ARF and drew transparencies of the lesions at fixed intervals over time. His drawings gave a very clear picture of the changing nature of the rash in a way no single photograph could. In 1944, Jones[5] named the presence of EM as one of the minor criteria of rheumatic fever. When the Jones criteria were revised in 1965 by the American Heart Association, EM was listed as one of the major manifestations of ARF, and no distinction was made between the variants of the rash.[6]

Manifestations

The individual lesions of EM begin as pink macules or papules that expand to form annular plaques with flat, slightly pigmented or pale centers. The border is usually fairly distinct, dull red, and expands rapidly to form rings, or the individual lesions may coalesce to form polycyclic lesions. The lesions may expand by 2 to 10 mm in 12 hours.[1] The borders may be delicate, flat or raised, reticulate or serpiginous. The individual lesions vary in size and number. The lesions are nonpruritic, despite an urticarial appearance in some cases.

Erythema marginatum is typically confined to the trunk and proximal extremities, sparing the face, hands, and feet. Mucous membranes are not involved, and the rash does not desquamate when it clears. The rash is often not noted by patients because of its rapidly changing nature, lack of cutaneous symptoms, and evanescence. Erythema marginatum may appear at any time during the course of ARF, but it is typically observed at the peak activity of carditis and arthritis.

The incidence of EM in ARF is between 5% and 15% in most series. The individual lesions of EM are transient, appearing and disappearing over several hours, but occasionally lasting a day or two. The lesions may appear after a warm bath. The duration of EM varies, with most cases lasting a few days. However, reappearances up to 2½ years after initial presentation have been recorded.[7] The rash may reappear after all signs of ARF have disappeared.

Histologic Findings

The earliest report of the histologic characteristics of EM was in 1935, when an active lesion was reported as showing "an acute inflammation of the outer and middle layers of the cutis with a well marked polymorphonuclear leukocytic infiltration."[1] Few additional histologic reports followed until 1983, when Troyer et al[1] described a case of perivascular infiltration of neutrophils in the papillary dermis with EM and suggested that this characteristic could help distinguish EM from some of the rashes with which it can be confused, particularly urticaria, erythema multiforme, and other figurative erythemas.

Genetics

There is no genetic predisposition to EM. The mechanism responsible for the appearance of the rash is still unknown.

Treatment

Erythema marginatum is unaffected by treatment of ARF with anti-inflammatory drugs or other agents. The eruption is not pathognomonic of ARF and has been described with bronchiectasis, nephritis, and tinea capitis. Recently, a case of psittacosis with "erythema marginatum-like lesions" has been described.[8] Erythema marginatum most commonly develops in individuals with ARF. With the resurgence of this disease in recent years, it is important for clinicians to recognize this elusive rash.

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Pathological Case of the Month

Andreas W. A. van Egmond, MD; Mary Ellen Peters, MD; Elaine H. Mischler, MD (Contributors);
Enid Gilbert-Barness, MD (Contributor and Section Editor)

A 13-month-old boy was referred because of persistent asymptomatic opacification of the left upper thorax. He had been well until age 7 months, when he developed a productive cough and fever and was admitted to the hospital because of left upper lobe (LUL) and right middle and right lower lobe pneumonia. Intramuscular antibiotic treatment resulted in resolution of symptoms and clearing of pneumonia in the right lung. However, the LUL opacification remained. Because the LUL infiltrate persisted (Fig 1) after a 5-week outpatient course of oral antibiotics and chest physical therapy, bronchoscopy and bronchoalveolar lavage were performed. Results of the examination revealed no abnormalities, and the infant was again treated with antibiotics on an outpatient basis. Three months later, computed tomography of the chest revealed a homogeneous mass in the left thorax (Fig 2). A wedge resection of a noninflating part of the LUL was performed (Figs 3 and 4).

The thoracic surgeon reported a gross abscess and adhesions to the mediastinum and parietal pleura. *Klebsiella* species were cultured from the specimen. Throughout the course, results of physical examination were unremarkable.

The infant's medical history was negative for bacterial skin infections, recurrent otitis media, lymphadenopathy, and gastrointestinal symptoms.

Results of renal ultrasonography, quantitative immunoglobulin electrophoresis, and tests of serum hemolytic complement were within normal limits, as was a roentgenogram obtained after ingestion of barium that was used to rule out bronchoesophageal fistula.

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Contributed from the Departments of Pediatrics and Pathology, University of Wisconsin Hospitals and Clinics, 600 Highland Ave, Madison.

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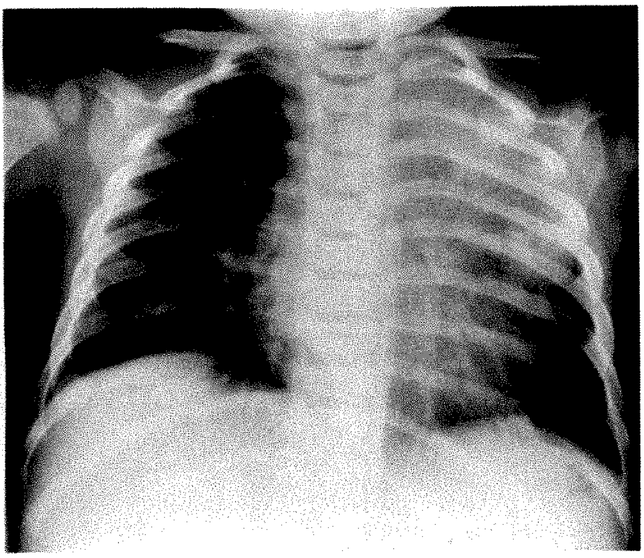

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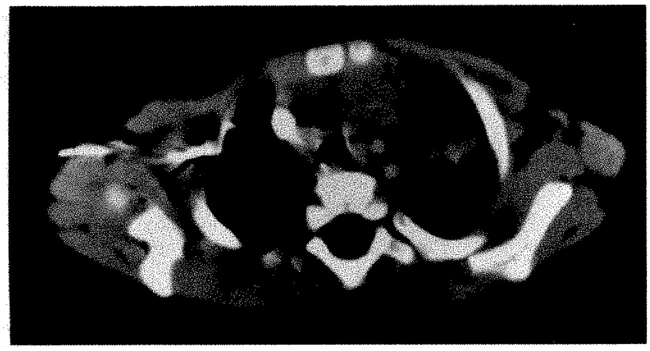

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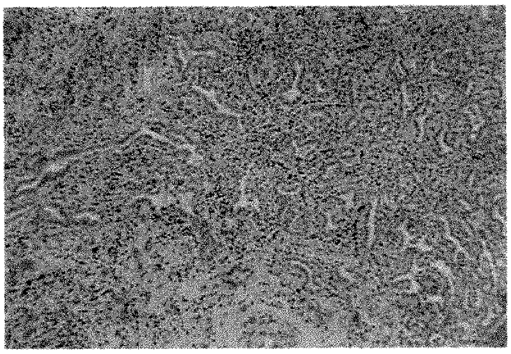

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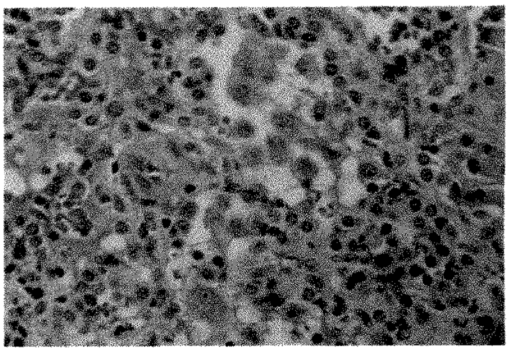

Figure 4.

Diagnosis and Discussion

Chronic Granulomatous Disease With Histologic Features of Pulmonary Sequestration

Fig 1.—*A chest roentgenogram demonstrates opacification of the left upper thorax, with an air bronchogram centrally.*

Fig 2.—*A computed tomogram of the chest obtained 7 weeks before surgical biopsy demonstrates a large mass in the left upper chest extending from the apex to the level of the hilum, the borders of which cannot be delineated from the left upper lobe. Consolidation is evident in the left upper lobe.*

Fig 3.—*Microscopic appearance of lung with dysplastic and immature bronchial elements resembling pulmonary sequestration with infiltrate of histiocytes and lymphocytes (hematoxylin-eosin, ×100).*

Fig 4.—*Microscopic section of lung with lymphocytic infiltration of histiocytes containing periodic acid–Schiff–positive material. Results are consistent with chronic granulomatous disease (periodic acid–Schiff, ×250).*

Results of nitroblue tetrazolium tests were repeatedly abnormal.

Chronic granulomatous disease is caused by genetic defects of phagocyte NADPH oxidase, the enzyme responsible for superoxide formation. This inability of the phagocytes to undergo the "respiratory burst" required for peroxidating and chlorinating the membranes of certain phagocytized bacteria and fungi leads to the inability to kill these pathogens.[1] Clinically chronic granulomatous disease is a syndrome of recurrent bacterial and fungal infections and granulomatous tissue reaction. Pyoderma, suppurative lymphadenitis, pneumonia with suppurative complications, peritoneal and enteral infections, liver abscess, osteomyelitis, and urinary tract infections are the more frequently encountered conditions at presentation, occurring in 73%, 73%, 81%, 46%, 29%, 21%, and 17% of patients, respectively. Generalized lymphadenopathy (74% of patients), hepatosplenomegaly (52% of patients), anemia, and hypergammaglobulinemia are also common.[2] The most frequently isolated pathogen is *Staphylococcus aureus* (52% of patients), followed by *Aspergillus* (40% of patients) and *Salmonella* (33% of patients). *Klebsiella* organisms are identified in 8% of patients.[2] The onset of first infection was within the first year in 71% of cases (mean, 16 months; range, 1 day to 16 years).[2] Five genetic variants have been described thus far. The most common variant is X-linked recessive and appears to be correlated with more severe infections than the autosomal recessive variants.[3] All four components (gp91, p22, p47, p67) of NADPH oxidase may be affected.[4]

The diagnosis is usually made when results of a nitroblue tetrazolium slide test demonstrate neutrophil inability to reduce nitroblue tetrazolium to blue formazan dye in blood. Results of lung biopsy show a nodular granulomatous reaction, with pigmented histiocytes containing lipofuscin (ceroid) that is periodic acid–Schiff–positive.

Treatment consists of administration of prophylactic antibiotics such as co-trimoxazole[2,5] and interferon gamma,[6] which have been proven to reduce the frequency of bacterial infections.

A pulmonary sequestration is defined as a mass of distorted, nonfunctional, pulmonary tissue that has no connection with the tracheobronchial tree and that receives its blood supply from anomalous systemic arteries. Intralobar pulmonary sequestration is invested by visceral pleura, as opposed to extralobar pulmonary sequestrations. Presenting symptoms include cough, hemoptysis, chest pain, feeding difficulties, recurrent pneumonias, fever, weakness, respiratory distress, and failure to thrive. Physical signs are frequently absent or nonspecific. Chest roentgenograms are almost always abnormal but nonspecific. Bronchoscopic examination is not helpful. An arteriogram helps identify the arterial supply. The final diagnosis is based on results of a biopsy showing a proliferation of immature bronchial elements in an inflammatory and dysplastic stroma.[7,8] Chronic infection may require surgery (lobectomy). Pulmonary sequestration is generally presumed to be congenital. However, Stocker[8] and Gebauer and Mason[9] propose a chronic inflammatory cause for some cases of intralobar pulmonary sequestration.

Prophylactic co-trimoxazole therapy was begun, and the infant had no further infectious complications.

Mrad et al[10] described a case of chronic granulomatous disease with *Aspergillus*-associated pneumonia and angiographic proof of systemic arterial supply of the affected area. We propose that chronic pneumonia secondary to chronic granulomatous disease may have caused the observed features of pulmonary sequestration in both their case and ours.

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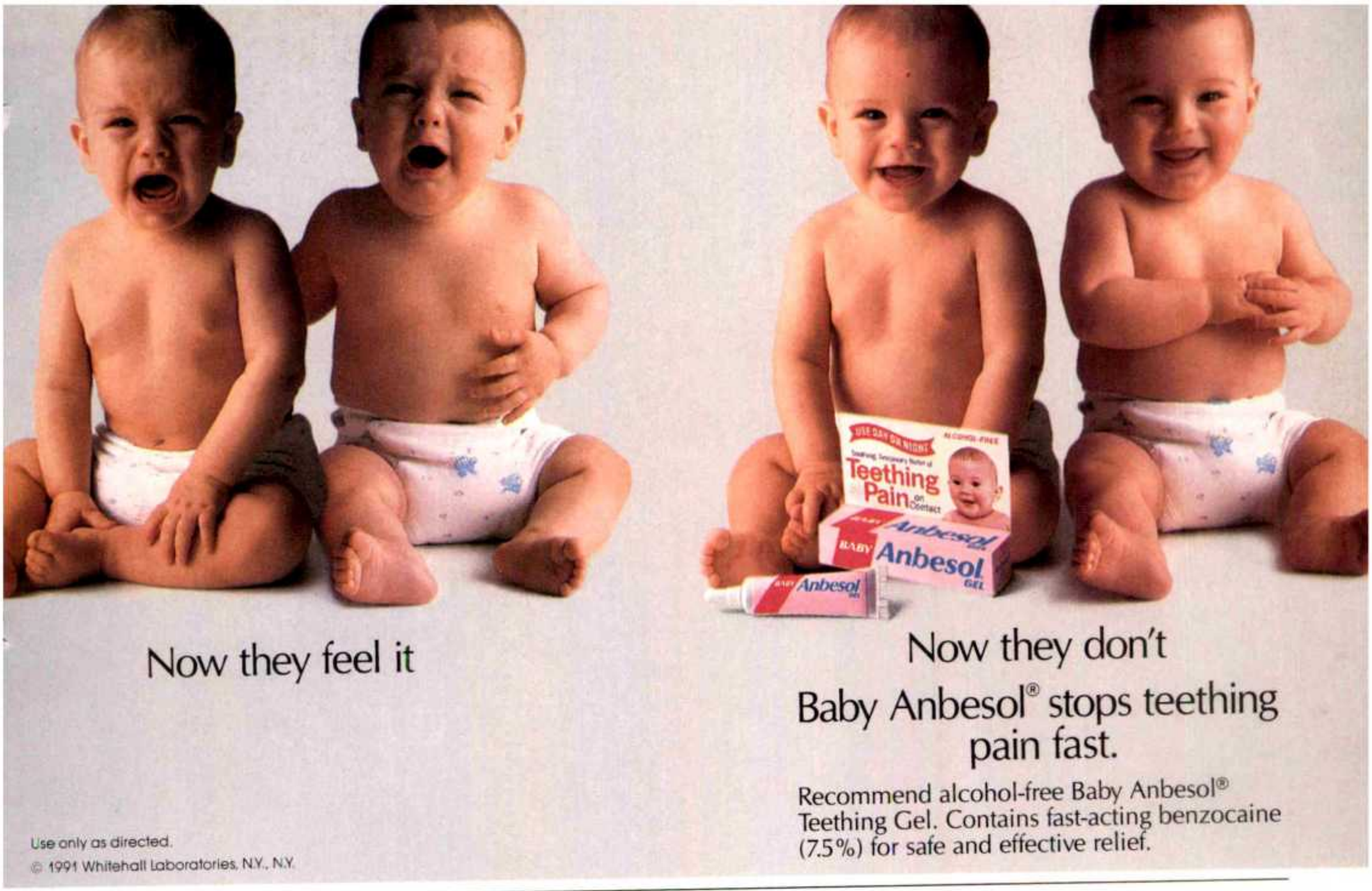

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See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage and Administration: The *Augmentin* 250 mg tablet and the 250 mg chewable tablet do *not* contain the same amount of clavulanic acid (as the potassium salt). The *Augmentin* 250 mg tablet contains 125 mg of clavulanic acid, whereas the 250 mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the *Augmentin* 250 mg tablet and the 250 mg chewable tablet should *not* be substituted for each other, as they are not interchangeable.

Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* 250 mg tablets are not equivalent to one *Augmentin* 500 mg tablet. Therefore, two *Augmentin* 250 mg tablets should not be substituted for one *Augmentin* 500 mg tablet for treatment of more severe infections.

Dosage: Adults: The usual adult dose is one *Augmentin* 250 mg tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* 500 mg tablet every eight hours.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and lower respiratory tract infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Severe infections should be treated with the higher recommended dose.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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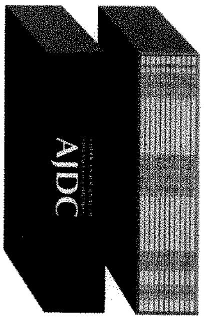

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Brief Summary

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were:
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Nausea

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

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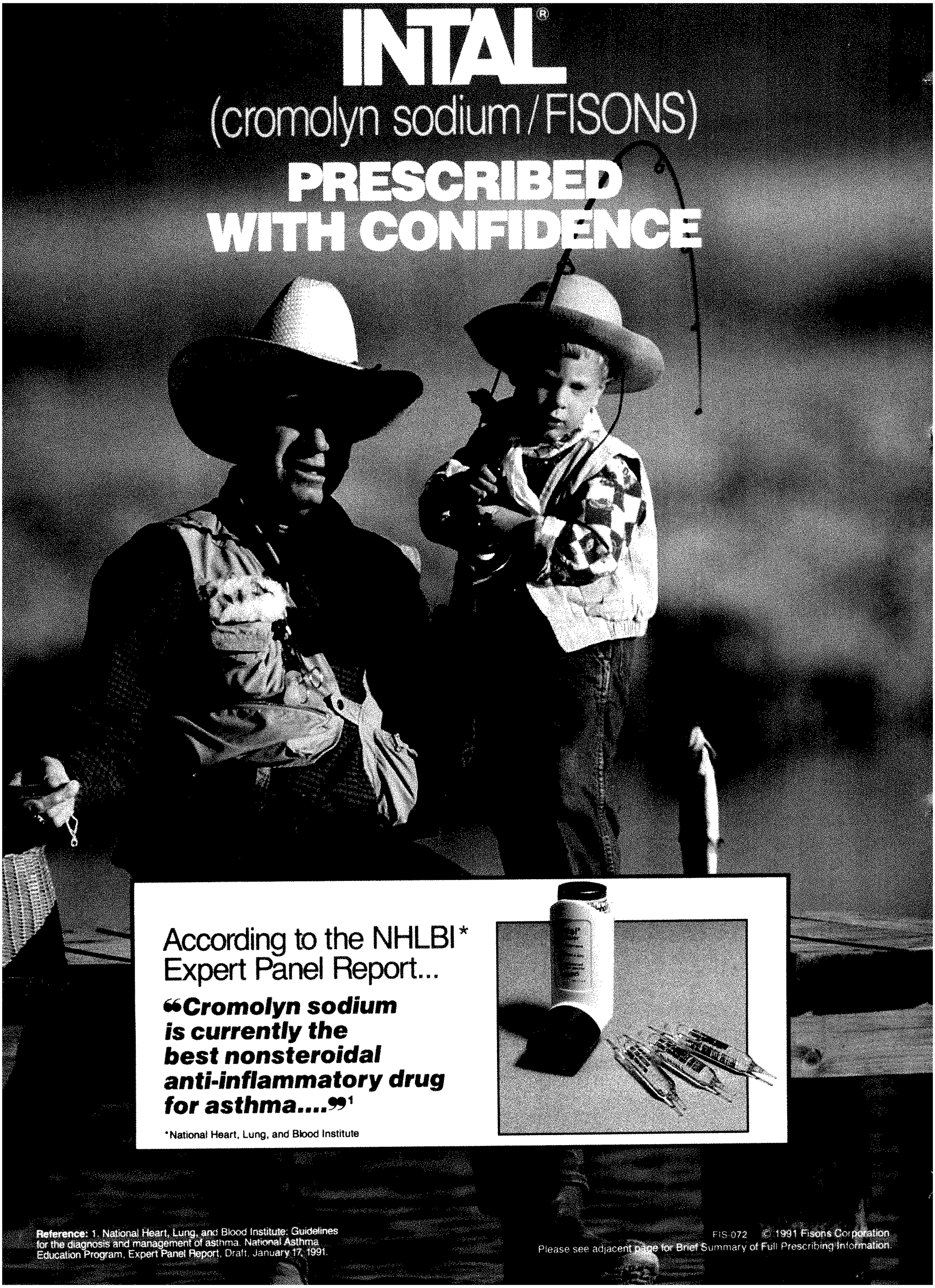

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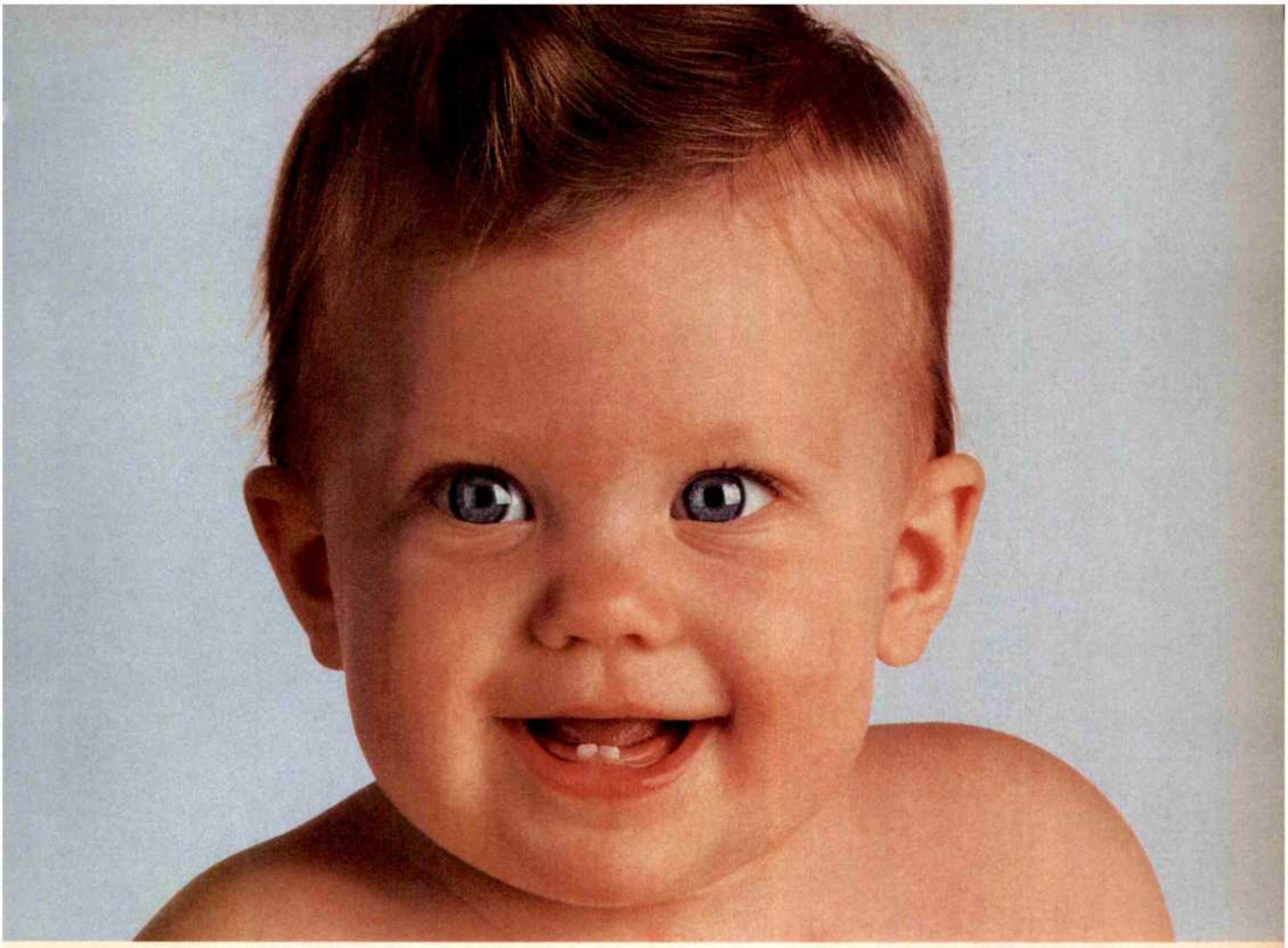

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*The Vi-Flor® Assure Program pays for repaired cavities submitted for reimbursement under the terms described in the Program Guide. Payment is up to $45 per tooth repaired, with a maximum lifetime benefit per child of $225. In some states, payment for cavity repair will be paid to the dentist administering cavity repair.

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Routine Vi-Flor® supplementation to help you guard appropriate patients against caries risk and nutritional risk.

INDICATIONS AND USAGE: VI-FLOR supplements help prevent vitamin deficiencies and dental caries in children and adults when fluoride in the water supply does not exceed 0.7 ppm.[1,2,3] TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron help protect against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid vitamin mixtures.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis (brown spots on teeth).
The bottle should be kept out of reach of children. Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.
ADVERSE REACTIONS: Allergic rash and other idiosyncrasies have been rarely reported.
DOSAGE AND ADMINISTRATION: Take as prescribed by your doctor or dentist.

Supplemental Fluoride Dosage Schedule (mg/day)*

	Concentration of Fluoride in Drinking Water (ppm)		
Age	<0.3	0.3-0.7	>0.7
2 wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride supplementation: Revised dosage schedule. *Pediatrics*. 1986;77(5):758-761.
**The Committee recommends that all breast-fed infants be evaluated shortly after birth to determine their need for fluoride supplementation. In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula. No fluoride is present in the water used to produce Ready-To-Use formula.

PRODUCT	FORM	SIZE	FLUORIDE mg/dose
POLY-VI-FLOR 0.25 mg	Drops	50 mL Bottle	0.25
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POLY-VI-FLOR 0.25 mg	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.25 mg with Iron	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.5 mg	Drops	50 mL Bottle	0.5
POLY-VI-FLOR 0.5 mg with Iron	Drops	50 mL Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 mL Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 mL Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 mL Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

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1. Hennon DK, Stookey GK, Muhler JC. The clinical anticariogenic effectiveness of supplementary fluoride-vitamin preparations – Results at the end of four years. *J. Dentistry for Children*. 1967(Nov); 34:439-443.
2. Hennon DK, Stookey GK, Muhler JC. The clinical anticariogenic effectiveness of supplementary fluoride-vitamin preparations – Results at the end of five and a half years. *Phar and Ther in Dent*. 1970(Oct); 1:1-6.
3. Hennon DK, Stookey GK, Muhler JC. Prophylaxis of dental caries. Relative effectiveness of chewable fluoride preparations with and without added vitamins. *J. Pediatr*. 1972(June); 80:1018-1021.

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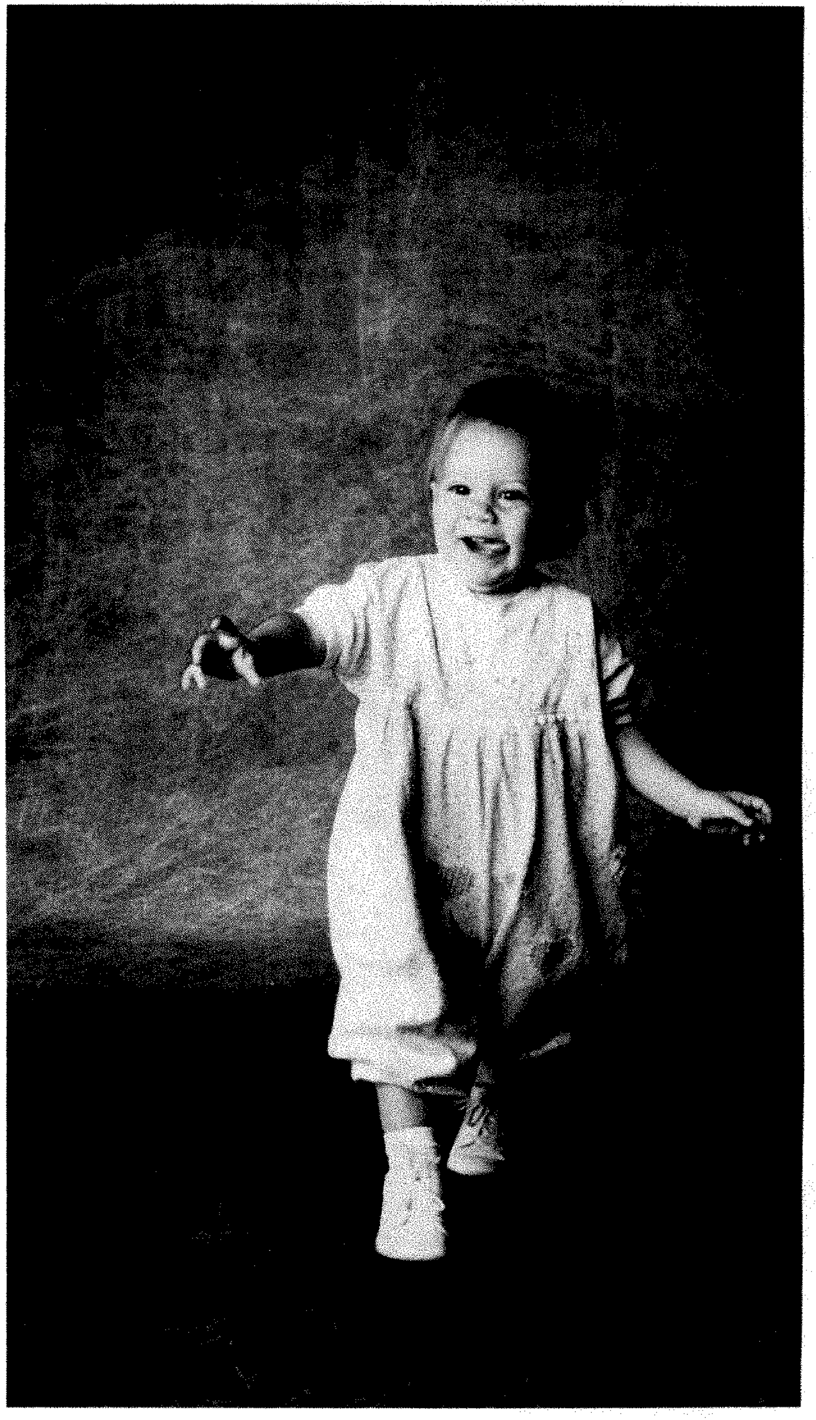

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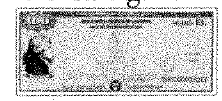

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100 mg/5 ml

Provides 6 to 8 hours of fever relief[1]

- **Effective fever relief is achieved with 2 levels of dosing:**
  - — 5 mg/kg for fevers under 102.5°F
  - — 10 mg/kg for fevers 102.5°F and higher
- **Pleasant tasting and easy to swallow**

Please see brief summary of Prescribing Information on the next page.

McNEIL

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Reference : 1. Walson PD et al. Ibuprofen, acetaminophen and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17

The following is a brief summary only. Before prescribing, see complete prescribing information in **Pedia-Profen** labeling.

INDICATIONS AND USAGE: Pedia-Profen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: Pedia-Profen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving **Pedia-Profen**, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Pedia-Profen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, **Pedia-Profen** should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **Pedia-Profen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **Pedia-Profen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Meaningful (3 times the upper limit of normal), elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with **Pedia-Profen**. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), **Pedia-Profen** should be discontinued.

Safety and efficacy of **Pedia-Profen** in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **Pedia-Profen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. *Adverse reactions occurring in 1% to 3% of patients:* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5 °F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: Pedia-Profen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—orange, berry-vanilla flavored

Bottles of 4 oz (120 ml) .... NDC 0045-0469-04
Bottles of 16 oz (480 ml) .... NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature.

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Hot Embers and Ashes as Sources of Burns in Children

Sir.—We recently reviewed our experience with a well-defined group of children to help identify the patient population at risk of thermal injury from contact with hot embers and ashes. Charts were reviewed for all children admitted to the Tampa Bay (Fla) Regional Burn Center between January 1986 and May 1991 who had been burned by hot embers or ashes. The following information was noted: patient sex and age, total body surface area burned, body parts burned, location of heat source, seasonal distribution of burn injuries, persons responsible for starting the fire, necessary treatment, need for grafting, presence of complications, length of hospital stay, and level of function after treatment.

Patient Reports.—Thirty-four children with burn wounds from hot embers and ashes were identified from medical charts. All were younger than age 16 years (median, 30 months; range, 11 months to 12 years 3 months). Twenty-four patients (71%) were younger than age 4 years. Twenty patients were boys, and 14, girls.

The median total body surface area burned was 3% (range, 1% to 17%). Burns primarily involved the distal extremities, with 24 patients having foot burns, 15 having hand burns, and seven having burns to both a foot and a hand. Four patients had burns to both feet and both hands. The seven cases of leg burns involved the lower leg or knee. Other areas of the body burned included the forearm (five patients), face (one patient), abdomen (one patient), and buttocks (one patient).

All of the children underwent immediate débridement on arrival to the burn center, followed by twice daily occlusive dressings with silver sulfadiazine cream. Eleven patients (32%) ultimately required split-thickness skin grafting. Two patients required amputation of fingers, and one patient underwent toe amputation. The median length of hospital stay was 5 days (range, 1 to 33 days).

Six patients (18%) had some degree of dysfunction at 2-month follow-up. All dysfunction involved hypertrophic scarring in one or more fingers or toes and were being managed with pressure garments and massage. Two of these six patients required additional hospitalization for scar contracture release.

Characteristics of the heat source are summarized in the Table. Burning brush was the heat source in 19 cases, followed by camp fires (10 cases) and barbecue coals (five cases). Eighteen patients were burned by embers or ashes from fires that were active at injury or within 24 hours of injury. Ten patients were burned by embers or ashes from fires thought to have been extinguished more than 24 hours before injury. Six children were burned by embers or ashes from fires of undetermined age that were not identified until the child's response to the burn was registered. Three of these six fires were fires buried on the beach, and three were buried brushfires.

The seasonal distribution of injuries showed the most burns to have occurred in spring (March through May; 13 burns), with almost an even distribution in summer (June through August; six burns), fall (September through November; seven burns), and winter (December through February; eight burns).

Examination of where the injury occurred in relation to the child's primary residence at injury showed that 21 children (62%) were burned at home; six, during camping excursions; three, at a beach; two at a neighbor's property; and two, at other locations. Fires started by a family member were responsible for 25 burns (74%). Four fires were started by a person known to the child, and five were started by an unknown person.

Comment.—Thermal injury from embers and hot ashes accounted for 15% of pediatric admissions to our regional burn center during the study period. Embers and hot ashes have been reported to account for up to 19% of all burns in children.[1-3] The age and sex distribution of the patients in our study were characteristic of those of most children suffering any type of injury. Most were boys younger than age 4 years, and injury was most likely to occur close to the family residence.[1]

Total body surface area burned was small in most cases and frequently involved a distal extremity. This pattern fits the scenario of the child walking into hot embers or ashes and either running out of the embers or ashes or falling and breaking the fall with the hands, which are then also burned. We were unable to ascertain how many of these children were wearing shoes, which may play a major role in prevention, especially in the temperate climate of Florida, where walking barefooted is common.

Injury to the distal extremities is particularly worrisome in children because extremities are in a state of rapid growth. Consequently, the burn may heal with a hypertrophic scar that requires surgical reconstruction during a period of several years. For these reasons, an aesthetically pleasing result and a normally functioning ex-

Characteristics of Heat Source*

Fire Type	Fire Active at Injury or Extinguished for <24 h Before Injury	Fire Extinguished for >24 h Before Injury	Age of Fire Unknown
Brushfire	8	8	3
Barbecue coals	4	1	0
Camp fire	6	1	3
Total	**18**	**10**	**6**

*Values are number of cases.

tremity may be difficult to achieve.[4] In our patient population, complications causing permanent disfigurement or loss of function were few. However, one third of the patients required skin grafting, adding significantly to the length of hospital stay.

Information obtained about circumstances of injury and characteristics of the heat source are disturbing. Fully 47% of these injuries resulted from heat sources believed to be no longer hot or not known to be present. Fires thought to be extinguished for more than 24 hours generally were responsible for burn injuries in spring and were typically set to burn cleared brush in the yard of the child's residence or an adjacent yard. In our county, Hillsborough County, Fla, and surrounding counties, this is a violation of the county fire code, which prohibits open burning of trash or brush. If fires are left to smolder overnight, the external layer of the fire cools. However, deeper layers are insulated and may harbor larger embers capable of producing a significant thermal burn. Covering the fire with sand or dirt can accentuate this effect and effectively hide it from the innocent bystander. This was evidenced in six of our cases and in those reported by Wiebe and Yamamoto.[5] In fact, two of our six patients were burned in separate incidents in the same sand-covered fire pit on the same day.

Another worrisome aspect of these burn injuries is the apparent breakdown in supervision in cases where the fire was started by a family member. Supervision by a responsible person is essential because young children are curious and generally less capable of recognizing and evaluating a potentially dangerous situation than are older children and adults.

These cases illustrate that strategies for preventing thermal injuries should include enforcement of existing fire codes as well as distribution of information about how to properly extinguish hot ashes and embers once the active flame is extinguished. Only when the ember is out will the potential for thermal injury be gone. Proper dousing of camp fires following the Boy Scout dictum of "make sure fires are COLD OUT" should be emphasized. *The Boy Scout Handbook*[6] suggests that if water is available it should be repeatedly stirred into the fire bed until all embers and the fire bed are cool enough to touch with one's hand. If water is not available, the pit should be stirred with dirt or sand and all embers rubbed into the dirt or smothered with dirt until the embers are cool enough to touch. Based on the information gathered in this study, we hope to develop a program similar to the "Cool Your Coals" program designed and proposed by Cartotto and coworkers.[2] Their program relies on an information campaign aimed specifically at injuries caused by camp fires and barbecue grills. A poster is made available to parents and children that contains information about fire safety. Posters are displayed and distributed by a number of different sources, including physicians, suppliers of outdoor and barbecue equipment, local and national campgrounds, and local newspapers. The program focuses on the peak outdoor season in an effort to influence the population at highest risk.

Using this information and the information gathered in our study, we can expand on the educational efforts of Cartotto et al to reach a rural population that burns brush and trash. Displaying information at local stores, schools, churches, and gas stations may be a more effective method of reaching people at risk. Increased awareness of the importance of local fire ordinances (which result in improved air quality and burn prevention) and improved enforcement of these ordinances may add to the success of the campaign by changing behavior. Use of child restraints and smoke detectors are good examples of what a campaign that couples enforcement of laws with public education can accomplish.

We suggest that pediatricians include in patient records family activities involving fire-making. Pediatricians should pay particular attention to families who burn brush or leaves or whose recreational activities include making camp fires. As with other potentially hazardous situations involving young children, nothing supersedes the need for close adult supervision.

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Water Intoxication

Sir.—In their interesting report on water intoxication in St Louis, Mo, Keating et al[1] wondered about the reason for the striking increase in its occurrence, suggested a national epidemiologic study, and proposed an increase in the amounts of free formula provided to infants living in poverty.

Of the mothers of the 31 infants described, only one was married, three were addicted to crack cocaine and alcohol, and 27 received their formula (plus "nutritional" advice that included giving water to the unsatisfied breast- or bottle-fed infant) from the Women, Infants, and Children program. If many mothers "presume that WIC provides everything the infant needs," it is because the advocates and operators of the program have so implied.

I wonder if any of these infants ever had the benefit of a pediatrician or family practitioner's counsel. It is a sad reflection on the state of our society that children are born into such circumstances and are then cared for by the huge bureaucracies that have been created for that purpose, giving canned advice or none at all with the free formula they dispense. It is painfully obvious that this has contributed to the decline in breast-feeding among participants. As to the demise of sources of additional free formula, I suspect that the zealous advocates of breast-feeding drove them away.

To the degree that the pediatric profession has allowed much of its role in the care of infants and children and in the guidance of teenagers to be usurped by social "scientists," activists, and politicians, we will continue to witness a slide in the direction of the disastrous policies that brought about the debacles of centrally planned societies. This "American epidemic" is a clear symptom of such deterioration in the quality of child care.

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[1] Keating JP, Schears GJ, Dodge PR. Oral water intoxication in infants: an American epidemic. *AJDC.* 1991;145:985-990.

Sir.—In the September 1991 issue of *AJDC*, Keating and colleagues[1] presented results of compelling, descriptive, epidemiologic research on the growing problem of oral water intoxication in infants.

The authors suggest that the unavailability of infant formula was a major factor in the increased occurrence of oral water intoxication and substantiated this conclusion with the fact that the current amount of formula supplied through the Women, Infants, and Children program is inadequate for the growing infant. Mothers simply supplement with water when the formula runs out.

We agree with the authors that more formula must be made available for poor infants and that care givers must receive better education about using formula. However, the obvious and most cost-effective solution to this serious health risk is the promotion and support of breast-feeding through infancy by all providers of maternal and child health care.

The superiority of breast-feeding for both infants and mothers needs greater emphasis in state-sponsored public health efforts. Breast milk cannot be diluted, and lactation promotes mother-child bonding. Greater prevalence of breast-feeding among participants of the Women, Infants, and Children program could lead to better use of available resources for pregnant and postpartum women and their children. It is no longer a choice between two equally acceptable forms of infant nourishment, especially where impoverished families are concerned.

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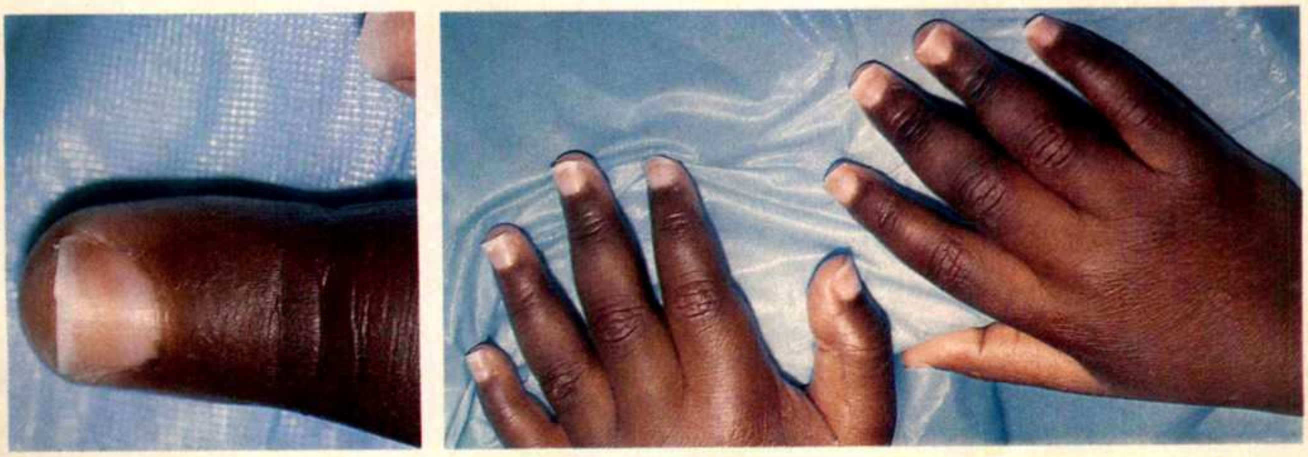
Nail-Bed Lines in Kawasaki Disease

Sir.—Kawasaki disease is a vasculitis of unknown etiology. It is usually accompanied by a febrile illness and occurs primarily in infancy and early childhood. Numerous associated clinical manifestations have been described. Reported mucocutaneous abnormalities have included oropharyngeal changes, polymorphous rash, and peripheral extremity changes. The latter have included erythema of the palms and soles, induration of the hands and feet, desquamation of the skin of the hands and feet, and Beau's lines.[1] Unusual red transverse nail-bed lines were observed in four of our patients with Kawasaki disease. No previous report of this clinical manifestation was found.

Patients and Methods.—All patients fulfilled classic diagnostic criteria of Kawasaki disease and were seen by the author between 1984 and 1990 either in the Pediatric Arthritis Clinic at the University of Kansas Medical Center or during inpatient consultations.[2]

Results.—Four of the 26 patients demonstrated red transverse nail-bed lines (Figure). The lines were present during the late acute phase or early convalescent phase and either preceded or accompanied fingertip desquamation. They persisted for a few days to 2 weeks. The lines did not blanch with pressure and did not become ecchymotic. They were located approximately halfway between the lunula and the edge of the nail. One of the four patients also had Beau's lines.[3] None developed coronary artery lesions during the first 6 weeks of illness, and there was no direct correlation between red transverse lines and other clinical or laboratory manifestations of the disease (Table). However, all four patients had at least one other manifestation of active inflammation when the lines were observed. These patients' red transverse lines were clinically distinct from nail changes described with other systemic diseases, including other types of vasculitis. They were also distinct from any extremity changes observed in scarlet fever or other *Streptococcus*-related illnesses.

Red transverse lines in Kawasaki disease.



Manifestations of Kawasaki Disease in Patients With Nail-Bed Abnormalities*

Patient No./ Sex/Age, y	Fever Lasting >5 d	Conjunctival Injection	Mouth Lesions	Extremity Swelling	Desquamation	Rash	Enlarged Lymph Nodes	Coronary Aneurysm	Beau's Lines	Anterior Uveitis
1/M/1.5	+	+	+	+	+	+	+	−	−	−
2/F/2†	+	+	+	+	−	+	−	−	+	−
3/M/10	+	+	+	+	+	+	−	−	−	+
4/M/8	+	+	+	+	+	+	−	−	−	−

*Plus sign indicates present, and minus sign, absent.
†Patient had disease relapse.

Comment.—Systemic disease in which unusual nail manifestations have been described include cirrhosis, renal failure, hypothyroidism, and argyria.[3-8] Still other nail abnormalities are less disease specific. The latter group includes Beau's lines, which are associated with matrix injury and have been described in Kawasaki disease as well as hyperthyroidism and epidermal necrolysis.[9] These lines consist of deep transverse grooves in the nails themselves that migrate from the cuticle to the edge of the nails as the nails grow.

The pathogenesis of the red transverse lines in these four patients is unknown. Because the lines occur during active inflammation and, in two of the four patients, were associated with other acute-phase extremity changes, they may be related to localized vasculitis or nail-bed hyperemia.

Although the lines were observed in only some patients, this clinical finding may be an additional clue to the diagnosis of Kawasaki disease, particularly for patients in whom other manifestations are evolving or who do not demonstrate all of the classic criteria for diagnosis. Because efficacy of therapy depends on early diagnosis and treatment, and because the risk of coronary artery aneurysms is present even in patients with an incomplete clinical presentation, all potentially helpful clinical signs should be carefully considered by the physician.

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Dietary Calcium and Bone Health

Sir.—I applaud the attempts of Chan et al[1,2] to estimate the influence of dietary calcium on bone health in children and adolescents. There has been a long-standing controversy about recommended levels of dietary calcium for children and adolescents. We recently conducted a study of calcium intake and epidemiologic characteristics of fractures in schoolchildren, and in analyzing the results came to some interesting conclusions. Some of the conclusions were similar to those expressed by Chan, and some were not.

Patients Reports.—In the island of Majorca, Spain, we selected three towns (Andraitx, Palma, and Felanitx) for study. We selected these towns because (1) the residents of each town had the same socioeconomic background; (2) since 1984 the fluorine content in tap water was always <0.5 mg/L; and (3) the water supplies in each town contained very different levels of calcium during the 7-year period for which data were available. In Andraitx, the mean calcium level was 283 mg/L, compared with 133 mg/L in Palma and 86 mg/L in Felanitx.

In all three towns, the migration rate was low (9% population gain in Andraitx, 10% population gain in Palma, and 4% population loss in Felanitx). So, we expected the calcium content of the water supply to have a long-term dietary effect because most of the children had lived in the same town since birth.

We conducted a survey on antecedents of fractures in 1308 schoolchildren, ages 11 and 14 years. In Andraitx and Felanitx, we studied all schoolchildren aged 11 and 14 years. In Palma, a larger town, we randomly selected 11- and 14-year-old children from one of every six schools.

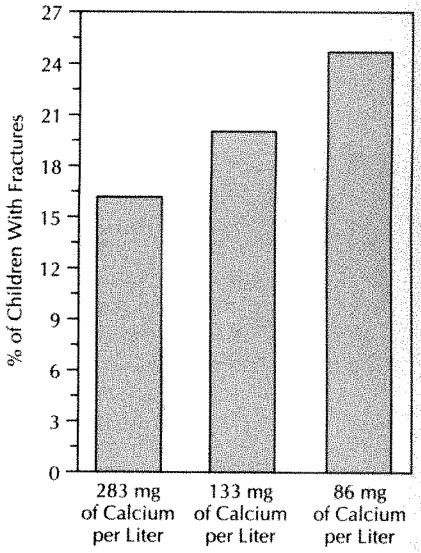
Results.—There was a significant difference ($P<.05$) in prevalence of fractures according to calcium content in the water supply of each town. This difference was particularly significant among 11-year-old children (prevalence of fractures, 8% in Andraitx, 14% in Palma, and 20% in Felanitx) (Table and Figure). Among 14-year-old children, the prevalence rates were more similar (22% in Andraitx, 24% in Palma, and 29% in Felanitx).

Comment.—Our results with 11-year-old schoolchildren were very similar to those of Chan: a high intake of calcium was associated with higher bone mineral content (BMC) and a lower risk of fractures. However, our results with schoolchildren older than age 11 years were quite different from those of Chan. Our results show that calcium intake was particularly important in the bone health of prepubertal children, but not as important to the bone health of pubertal children. Perhaps during adolescence the enormous increase in weight and height becomes the outstanding factor in bone formation. Increased participation in sports during puberty may also be a factor, as it is well known that physical activity affects bone metabolism and risk of fractures.

Prevalence of Fractures in Three Spanish Towns With Different Amounts of Calcium in Drinking Water*

	Andraitx	Palma	Felanitx
11-year-old children			
Fractures	5 (8)	46 (14)	33 (20)
No fractures	53 (91)	281 (86)	135 (80)
Total	**58 (100)**	**327 (100)**	**168 (100)**
14-year-old children			
Fractures	17 (23)	119 (24)	55 (29)
No fractures	58 (77)	373 (76)	133 (71)
Total	**75 (100)**	**492 (100)**	**188 (100)**
11- and 14-year-old children			
Fractures	22 (17)	165 (20)	88 (25)
No fractures	111 (83)	654 (80)	268 (75)
Total	**133 (100)**	**819 (100)**	**356 (100)**

*Amounts of calcium in drinking water were as follows: 283 mg/L (Andraitx), 133 mg/L (Palma), and 86 mg/L (Felanitx). Fifty-six percent of subjects were boys, and 44% were girls. Values are number (percentage) of subjects.



Association between calcium content in water and prevalence of fractures in 11- and 14-year-old children.

Some of Chan's results were similar to ours, prompting us to be more cautious about benefits of calcium intake in children older than 11 years. In Chan's earlier article,[2] a case-control study of BMC in 17 children aged 2 to 12 years who suffered accidental fractures, he found that the BMC of these children was lower than the BMC of the control group. But, in the group with fractures, two children were older than 11 years (aged 12 years) and had higher BMCs than did control subjects. Could BMC protect against fractures in toddlers, which are mostly the result of accidental falls, but have less of a protective effect in adolescents, whose fractures are usually the result of trauma, such as traffic accidents or sports mishaps? In his recent paper,[1] Chan stated that only 15% of children older than 11 years received the recommended dietary allowance (RDA) of calcium. His table showed that the daily intake of calcium in 12- through 14-year-old children was not lower than the intake of younger children, but higher. Despite this, older children did not meet the RDA because the RDA for calcium is higher starting at age 11 years. The National Research Council[3] explained that this recommendation is based on the rate of absorption in adults, and that the intestinal absorption of calcium in adults is less efficient than it is in children. My questions to Chan are: Does it make sense that 85% of children older than 11 years do not meet the RDA for calcium? Is so much calcium really necessary at this age?

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In Reply.—I read with interest Dr Verd and colleagues' comments regarding our article.[1] They have documented the association between calcium content in water and the prevalence of fractures in 11-year-old children. However, they did not find a similar association in 14-year-old children and wonder if calcium intake is important in older children. During puberty, growth accelerates and calcium needs increase. I and my colleagues believe that without adequate amounts of calcium, teens are at risk of low BMC. We have reported both low bone mineral status in lactating teenagers who did not receive adequate dietary calcium[2] and the positive effects of adequate dietary intake of calcium in these lactating teenagers.[3] We are now investigating the effects of dietary calcium on the bone status of 9- to 13-year-old girls.

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Health Care for Poor Children in the United States: A Full-time vs Part-time Solution

Sir.—Recently, the issue of providing primary health care for poor and uninsured or underinsured patients has received much attention in the medical literature. According to an *Index Medicus* search, in 1990 alone, there were 117 articles published in medical journals regarding health care for these patients. The attention is justified, because the problem of providing access to primary care for indigent patients, particularly indigent pediatric patients, is monumental. Between 30 and 40 million Americans lack health insurance, either public or private, and one third of these are infants and children.[1-3] According to the National Health Interview Survey, only two thirds of all poor children under age 6 years had some type of health insurance in 1986, with less than one half of the insured covered by Medicaid.[4] Children who lack health insurance have decreased access to care, use fewer health services, and are more likely to have adverse health outcomes.[5,6]

Obviously, one of the solutions to this problem is to increase the percentage of Americans with health insurance. An entire recent issue of *AJDC*[7] presented several different health insurance proposals as potential solutions for uninsured "Poor Children in the US." An important additional solution would be to increase the amount of physician services available to the uninsured poor. In a recent article in *JAMA*,[8] a recommendation was made for private physicians to "allot a minimum percentage of [their] practice to care for medically indigent and Medicaid patients." Similarly, many of medicine's professional associations have advocated that private physicians help to alleviate the problem by contributing free services to the poor. James E. Davis, MD, in his inaugural address as AMA President in 1988, challenged "every physician in America—whether in practice, education, research, administration, or in any endeavor—to tithe . . . time for the benefit of the American people. Just one tenth of the normal work week, 4 hours a week serving the public. . . ."[9] George Lundberg, MD, Editor of *JAMA*, made a similar request by recommending that all physicians work "50 hours for the poor" per year as part of their professional responsibility.[10]

While private physicians work part-time to address the access-to-care problem, physicians in public practices do so on a full-time basis. Physicians in community and neighborhood health centers, migrant health centers, the National Health Service Corps (NHSC), public health departments, the Indian Health Service, primary-care clinics in public general hospital outpatient departments, clinics for the homeless, and other public settings work full-time delivering primary care to medically indigent Americans. At present, there are approximately 1000 physicians in the NHSC and 410 physicians in the Indian Health Service of the US Public Health Service (unpublished data, Region VIII Office US Public Health Service, Denver, Colo, August 1991). In addition to these community-based Public Health Service physicians there are full-time physicians who work in public clinics in state, county, city, and nonprofit facilities. All these physicians work in salaried positions and provide primary care almost exclusively for poor, uninsured, and underinsured patients and families. To those of us who work in public practices, 50 hours of care represents 1 week, as opposed to 1 year, of service for the poor.

Solving the complicated problem of providing health care for uninsured patients will require much creativity. The solution to this problem lies both in expanding the availability of health insurance for indigent patients and families and in increasing physician services accessible to the uninsured poor. To accomplish the latter, we should encourage private physicians to provide uncompensated services. Even more importantly, we should expand the base of salaried, non-fee-for-service public physicians who work full-time to provide care for the poor. These physicians are in a unique position to be familiar with and coordinate an array of health and social services for disadvantaged populations in an integrated public health setting. They are able to relate to and address the financial, social, legal, and cultural concerns of their patients and are geared to patients' specific problems, including "poverty, stress, substandard housing, substance abuse, depression, divorce, and malnutrition."[11] By coordinating and expanding public practices with full-time physicians, we will continue to develop an infrastructure of care to make health services available to the poor, whether publicly insured or uninsured.

To significantly increase the number of full-time physicians in public practices, the following are suggested:

1. Reserve a certain percentage of every medical school class for premedical students with a demonstrated interest in public medicine. Select these students, provided they meet academic standards, because of their concern for and interest in providing care for indigent patients. Offer special preclinical course work and clinical rotations to prepare them to work in public practices.
2. Expand programs such as the federal NHSC Scholarship Program and similar state programs to attract medical students to careers in public medicine. Students in the NHSC Scholarship Program receive tuition and a monthly living stipend while in medical school and, in return, work in underserved communities on a year-for-year payback when they complete their residency training. Students and residents in the NHSC Scholarship Program and similar state programs should receive intensive training in, and exposure to, issues regarding the care of poor patients and families and to the concepts of community-oriented primary care[12-14] while they are in medical school and residency. This will improve their preparation for community service and could help to retain them in these communities after completing their obligations.[15] In addition, the NHSC Scholarship Program affords minority and other medical students who might otherwise not be able to afford the high cost of medical school an opportunity to obtain a medical education. These students may have a heightened sensitivity and concern for the plight of the indigent and may be willing to consider a career in public medicine at the completion of their NHSC obligation.
3. Introduce all medical students to this important issue at an early phase of their careers by providing course work on the problem of providing care for the poor and the concepts of community-oriented primary care in the preclinical curriculum of every medical school. Teach community medicine as a discipline by requiring at least one rotation in a clinic or hospital that provides care mostly to poor patients for students in the third and fourth years of medical school. This rotation should contain lectures and reading material that

highlight the special needs of the poor. These efforts will expose students to indigent care issues and, ideally, will encourage some of them to pursue a career in public medicine.

4. Develop more primary-care residencies providing training for house officers who want to practice in public facilities. In the same way that residency programs have developed special tracks such as "Primary Care Tracks," residency programs should develop "Underserved Populations Tracks" to train residents who are interested in practicing in underserved areas when they complete their training. Target funding awards for primary-care training grants to residency programs that have demonstrated linkages with community health-care sites and services for the poor.

5. Expand the NHSC Loan Repayment Program as a way to get physicians to practice in underserved areas and to provide newly trained physicians with exposure to public practices in underserved communities. Physicians in this program work in sites caring for the poor and receive annual payments, in addition to their salary, directly toward the reduction of their student loans. Look carefully at the selection and site placement of both NHSC scholarship and loan repayment students and residents to assure that the participants are committed to primary care and that a good fit exists between the provider and the clinical site. Carefully address the professional needs of the NHSC physicians in these sites to improve the possibility of retaining them after they complete their obligations.[15]

6. Professional associations should devote additional attention to the problem of providing health care to poor patients by increasing the coverage of the issue in journals, adding appropriate educational and research sessions at meetings, and encouraging the development of sections within their associations that are specifically concerned with issues regarding care for indigent patients.

7. Form a specialty association for physicians in full-time public practice. Create a journal as a mechanism for communicating between these front-line practitioners of community medicine. At meetings of this group, research presentations on successful programs, educational sessions, and legislative and lobbying activities should address issues pertinent to providing care to the poor. Encourage research efforts through this association in areas of significance to indigent care, including "pathophysiology of poverty, health services, quality assurance, epidemiology, program evaluation, behavior and other areas."[16] These activities will increase the camaraderie, credibility, and professional recognition of physicians who choose to pursue a career in public medicine.

8. Remunerate physicians in public practices competitively for the work they do. This would reduce the financial constraints that often dissuade young physicians from pursuing a career in public medicine.

The problem of providing high-quality and accessible health care to the poor is the single biggest issue confronting the medical profession today. Fitzhugh Mullan, MD, recommends, "Much needs to be done to unite the disparate elements of clinical community medicine in order to make it the permanent and creditable part of the American medical system that it should be."[17] If we attract capable and idealistic students at the medical school level, provide them with appropriate community-oriented education and training, and have an adequate number of well-staffed community sites available for employment after their residencies, we should be able to greatly increase the amount of physician services available to the poor. Our ability to provide aggressive and reasoned solutions to this problem may determine our future recognition and success as a profession. As important as increasing the number of insured patients is developing a delivery system that includes full-time physicians dedicated to serving the poor.

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Kiss: A Developmental Milestone or a Culture-Determined Skill?

Sir.—Kissing is a complex gesture and has been considered part of the developmental process. Toward the end of infancy, the child shows increasingly greater capability to handle integrated actions. A gesture becomes the vector of organized thought. The perceptual-motor functions of the child begin to have potential application to many situations and assume the characteristic sociodramatic nature of the world in which he or she lives.[1] Training through education or imitation plays a dominant role in the learning of complex gestures like kissing, naming a body part, or blowing the nose.

True kissing is the ability of the child to press the lips on cheeks with or without sound, on verbal request. It is a complex gesture. Dargassies[2] has shown that 15% of children at age 12 months and 95% of children at age 15 months attempt to kiss; 24% of children at age 15 months and 40% of children at age 18 months give a true kiss. In our own ongoing studies on neurodevelopment of normal infants, we have found that after age 12 months, affectivity reactions are powerful. Children feel impelled to kiss and this is a major development at this period. About 30% of infants can understand what a kiss is and accordingly bring cheeks near to receive a kiss. By age 15 months, 60% of children can lick with lips on cheeks in an attempt to perform a kiss, with 20% able to give a real kiss. By age 18 months, the majority of children (75%) give a true perceptible kiss.

Apart from experience and training, which greatly determine the learning and perfection of this act, there are a lot of cultural connotations involved in the learning or teaching of the gesture itself. In our study, some of these aspects were explored and the following facts revealed: mothers usually felt uncomfortable if the child kissed a stranger, even if that happened to be another child. This uneasiness related mostly to aspects of hygiene. Mothers preferred the child kissing his or her own image in a mirror than a human being or doll and reasoned that the child was immensely happy at the narcissistic act and, thus, they encouraged it. All mothers welcomed the child giving a kiss rather than receiving one.

There was no difference between boys and girls in either giving or receiving a kiss. However, infants who had older siblings learned how to kiss slightly faster than the first-born child. An alternate form of kissing called the "flying kiss" in which the child kisses his or her own hand and blows the kiss out to the receiver is a more complicated gesture than the true kiss. A large number of children (65%) did attempt a flying kiss by age 18 months, although they failed to blow effectively.

It would be of interest to know whether kissing is a developmental milestone, involving an integrated nervous system and seen uniformly in all children, or merely a cultural acquisition. It is difficult to accept either of these views entirely. Whether cultures differ significantly in the acquisition of the skill or whether there are cultures in which this behavior is absent can be determined only by cross-cultural studies. Such data could probably tell us whether environment takes precedence over cerebrum in the development of the skill.

It appears that environment may have a greater role in the acquisition of the kissing skill since it is learned by imitation. However, it needs to be emphasized that no normal child ever attempts this behavior despite training before age 12 months. There is evidence of the need for intact cortical development, which demands synthesis of affect and behavior. Kissing has been used to test apraxia in neurologically impaired adults. It remains to be seen whether it can be used for the developmental assessment of infants.

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CORRECTION

Incorrect Number.—In the article entitled "Effects of a Night-Float System on Resident Activities and Parent Satisfaction," published in the March 1992 issue of *AJDC* (1992;146:307-310), an incorrect number appeared in the "Comment" section. The last sentence in the second paragraph of the right-hand column on page 309 should read, ". . . worth having to work nights rather than days during the 2 weeks they served as night-float residents during the senior year."

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Other viruses (including poliovirus and other enteroviruses) may compromise the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis. **Records Required by the National Childhood Vaccine Injury Act:** Manufacturer and lot number of vaccine administered must be recorded by health care provider in vaccine recipient's permanent record, along with date of administration and name, address, and title of person administering vaccine.

Health care provider must report to a health department or to the FDA the occurrence following immunization of any event set forth in the Vaccine Injury Table including: paralytic poliomyelitis — in a nonimmunodeficient recipient within 30 days of vaccination — in an immunodeficient recipient within 6 months of vaccination; any vaccine-associated community case of paralytic poliomyelitis; or any acute complication or sequela (including death) of above events.

Use in Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with Poliovirus Vaccine Live Oral Trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. A large retrospective study suggests that OPV may be temporally associated with Guillain-Barré syndrome. A causal relationship has not been established. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts.

The Centers for Disease Control report that during the years 1973 through 1984 approximately 274.1 million OPV doses were distributed in the US. During this same period, 105 vaccine-associated cases were reported (1 case per 2.6 million doses distributed). Of these 105 cases, 35 occurred in vaccine recipients (1 case per 7.8 million doses distributed), 50 occurred in household and nonhousehold contacts of vaccinees (1 case per 5.5 million doses distributed), 14 occurred in immunodeficient recipients or contacts, and 6 occurred in persons with no history of vaccine exposure, from whom vaccine-like viruses were isolated.

Thirty-three (94%) of the recipient cases, 41 (82%) of the contact cases, and 5 (36%) of the immune deficient cases were associated with the recipient's first dose of OPV. Because most cases of vaccine-associated paralysis have occurred in association with the first dose, the CDC has estimated the likelihood of paralysis in association with first v subsequent doses of OPV, using the number of births during 1973-1984 to estimate the number of first doses distributed, and subtracting this from the total distribution to estimate the number of subsequent doses distributed. This method estimates a frequency of paralysis for recipients of 1 case per 1.2 million first doses v one case per 116.5 million subsequent doses; for contacts, one case per 1 million first doses v one case per 25.9 million subsequent doses; with an overall frequency of 1 case per 520,000 first doses v 1 case per 12.3 million subsequent doses.

Other methods of estimating the likelihood of paralysis in association with OPV have been described. Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults 2 doses of enhanced potency IPV a month apart before the children receive ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the second dose of enhanced potency IPV. A booster dose of enhanced potency IPV can be given to partially immunized adults at the same visit that the first dose of OPV is given to the child. The adult should be informed of precautions, such as handwashing after changing diapers.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults…[with IPV]…before giving OPV to the child."

The American Academy of Pediatrics and the American College of Physicians have made similar recommendations.

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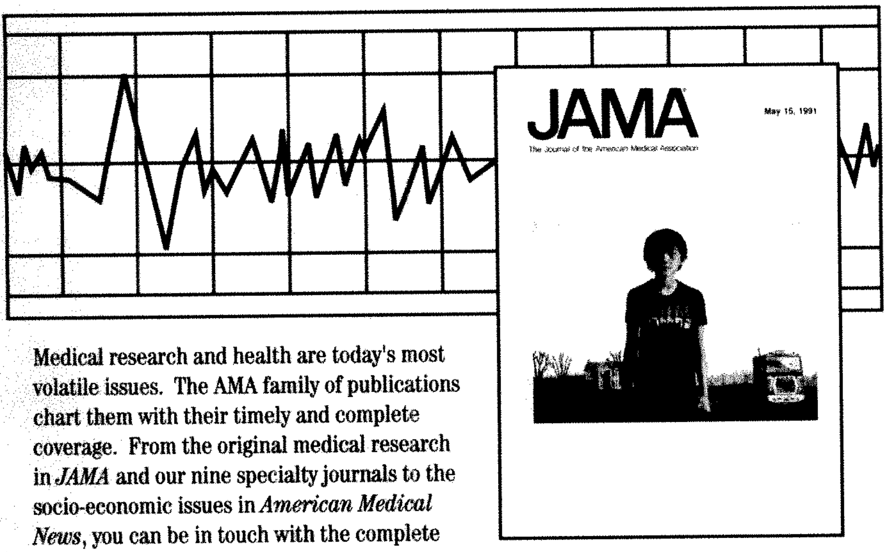
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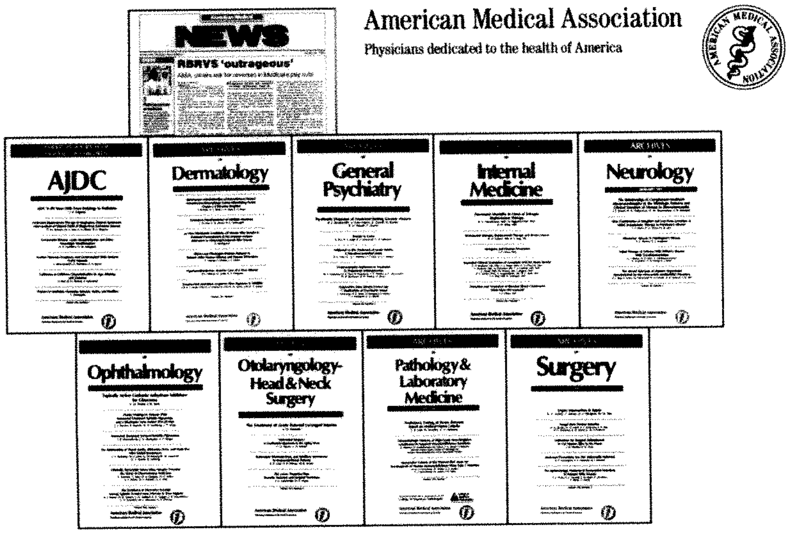

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EDITORIAL

Violence and Children in the United States

Violence has become an everyday fact in our lives. From the moment we awaken and are greeted by the daily newspapers and listen to the radio or television news accounts, we are reminded of the violent society in which we live. Those of my generation know the difference between now and "then." As a youngster, I could roam the streets of my neighborhood in Philadelphia without fear of bodily harm, and could run short- and long-distance tasks walking or using public transportation without fear of theft or injury. Many of my age can recite similar nostalgic recollections. But nostalgia cannot change the current situation. We are confronted with a reality that is frightening for many of our youth.

See also pp 677 and 683.

In this issue, we publish several reports on the status of violence in some parts of the United States. This is part of the efforts of the American Medical Association's family of journals to highlight this aspect of our current societal milieu. These reports paint quite a different picture of the environment in which some children attempt to grow and develop from that of a bygone era. For example, Meehan and O'Carroll[1] describe gang-oriented culture in Los Angeles and relate it to homicide. Their data tend to dissociate drugs and drug-related crime from the deaths of youth; rather, gang-related activities appear to have an inherent violent aspect that results in death among members and those unfortunate enough to be "in the way" of gang-related activities.

Sheley and coworkers[2] report how violence is transported into the schools in 10 inner-city schools in five cities in four states. Guns, so prevalent in the surrounding neighborhoods of inner-city schools, are one of the instruments of violence and death within the schools. One frightening aspect of both reports is that of randomness; in the report by Sheley et al, one in 10 victimizations appears to involve the innocent bystander. One might expect certain precautions and behaviors to help avoid direct contact with violent persons, but one cannot protect against or avoid the random violent act that affects one irrespective of whether precautions have been taken.

These reports indicate that many of our youth live in violent surroundings. They are forced to work, play, attend school, and conduct normal activities among persons and settings that not only condone violence but have adopted it as a way of life, and this is just the tip of the iceberg. In addition to violence experienced in the school and neighborhood setting, the home is no longer a secure haven for many. Familial abuse, member against member, is also rampant. *AJDC* has published a number of reports in the past on child abuse and neglect, exploring this element of violence and its effects on growth and development.[3-9]

Further, children are exposed to violence in the media, most notably, television and cinema.[10-13] Cartoons, dramas, the news, and even comedy and musical programs project images of violent behavior, often graphically and many times gratuitously. Some have felt that the effect of these depictions is to inure the child to violence at least, and to serve as acceptable models for behavior at worst.

The picture that emerges for some of our children is that they are awash in a sea of violence—at home, in the neighborhood, in school, and in the media. It is not surprising that many resort to violence themselves, and perpetuate what has been their own experience of interpersonal interaction or modeled in the media.

Much of what has been written is descriptive, ie, it tells us what is occurring. Little has been suggested to prevent or "cure" violence in the home or in society. We almost appear to be paralyzed by the problem, without ready solutions apparent. What can be done? What can we do as physicians?

Most will admit that the problem is societal, and medical intervention is but a small fragment of the potential solutions. Poverty, drugs, unemployment, and all of the other ills rampant in our society are progenitors of violence. Until we, as a total society, successfully address these issues, violence will continue to be part of our world. However, that does not mean that we have no active role to play. As physicians we can be alert to evidence of violence in our patients. Once detected, we should not ignore the signs and should take whatever social actions are available in our community.

As pediatricians we will most often encounter violence in a family setting; child abuse, neglect, and evidence of physical abuse of our patients or their caretakers should all be reported to the appropriate social agencies, including the police departments. We can also act in concert with our professional societies. The Rochester Pediatric Society has taken a stand on gun safety. Through its Gun Safety Task Force, a report entitled *Gun Safety Guidelines* was widely circulated. This brochure offers advice to parents in an effort to protect children in that community. In 1990, during a single 10-day period, five Monroe County, New York, children were accidentally wounded by guns; three were seriously hurt and one was paralyzed. These events stimulated the Rochester Pediatric Society to play a more active role in prevention via the brochure and a comprehensive educational campaign aimed at pediatricians and, through them, parents (James Sayre, MD, personal written communication, February 1992). Other professional groups may wish to take similar actions in their own areas.

As citizens we should actively support groups in society that seek to improve the factors that contribute to violence. For example, we should be active advocates for reduced violence in children's television programming. We should advocate gun control to prevent accidental or deliberate use of handguns to kill or maim children. We can educate our communities about the dangers of guns, advocating elimination of guns in the household or, at a minimum, safe practices. We can also take a more vigorous political role in advocating gun-control legislation.

We can also instruct parents in their role in monitoring children's television-viewing habits. We can assist school boards, principals, and teachers of the schools in our districts in their attempts to reduce the violent environment in their arenas. These may seem small, even futile, steps in a problem that appears to overwhelm society, but many such small interventions may add up to effective action in a neighborhood, a school, or even an entire community.

Violence threatens to supersede illness as a cause of pediatric morbidity and mortality in some communities. We must first understand it and then take whatever actions we can as professionals and citizens to help control, and eventually eliminate, it from the lives of our patients. The American Medical Association has taken a first step in casting a light on the extent and nature of violence in our society. Let's join forces now to see if we can reduce violence and halt its impact on our youth.

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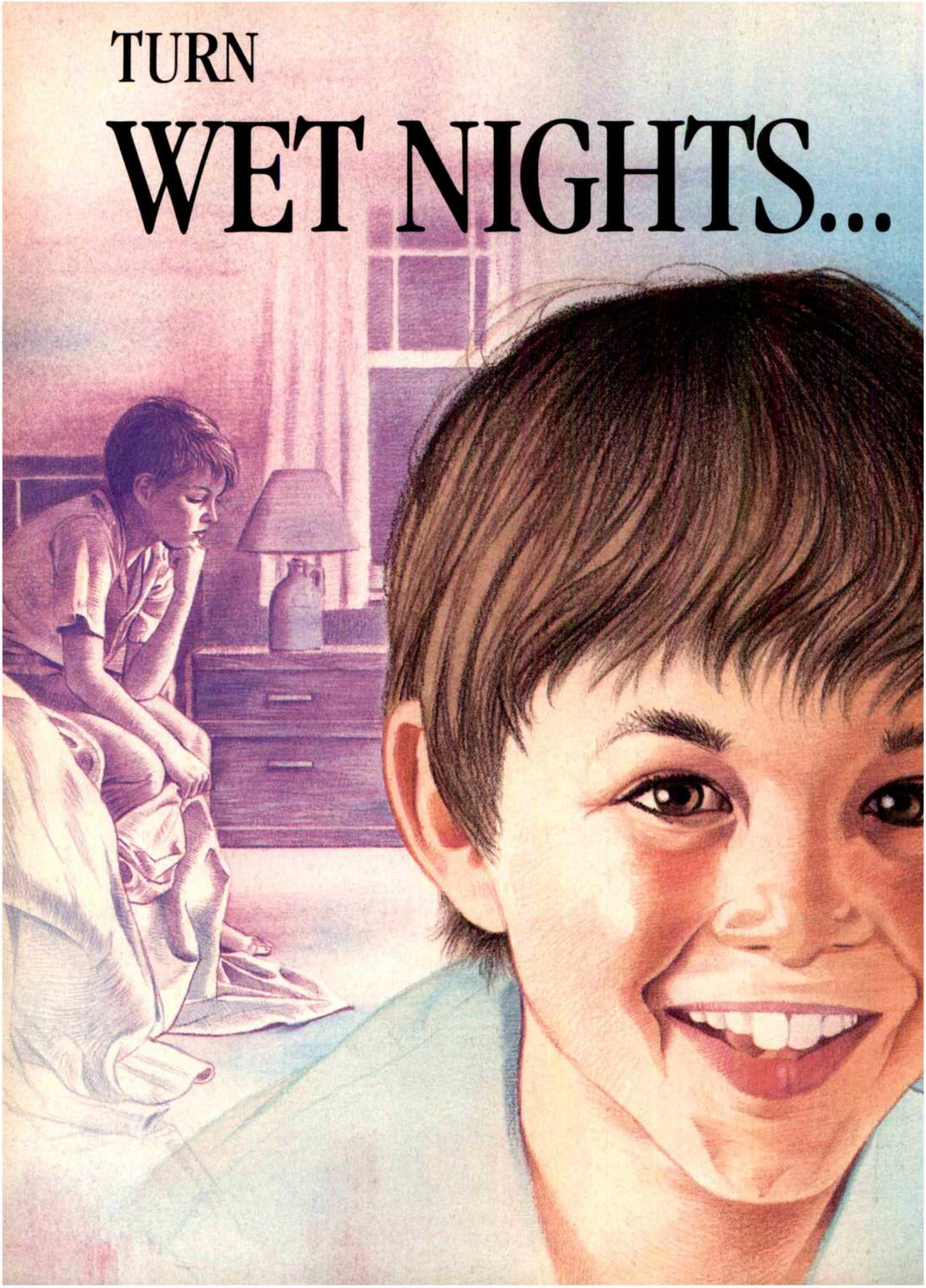
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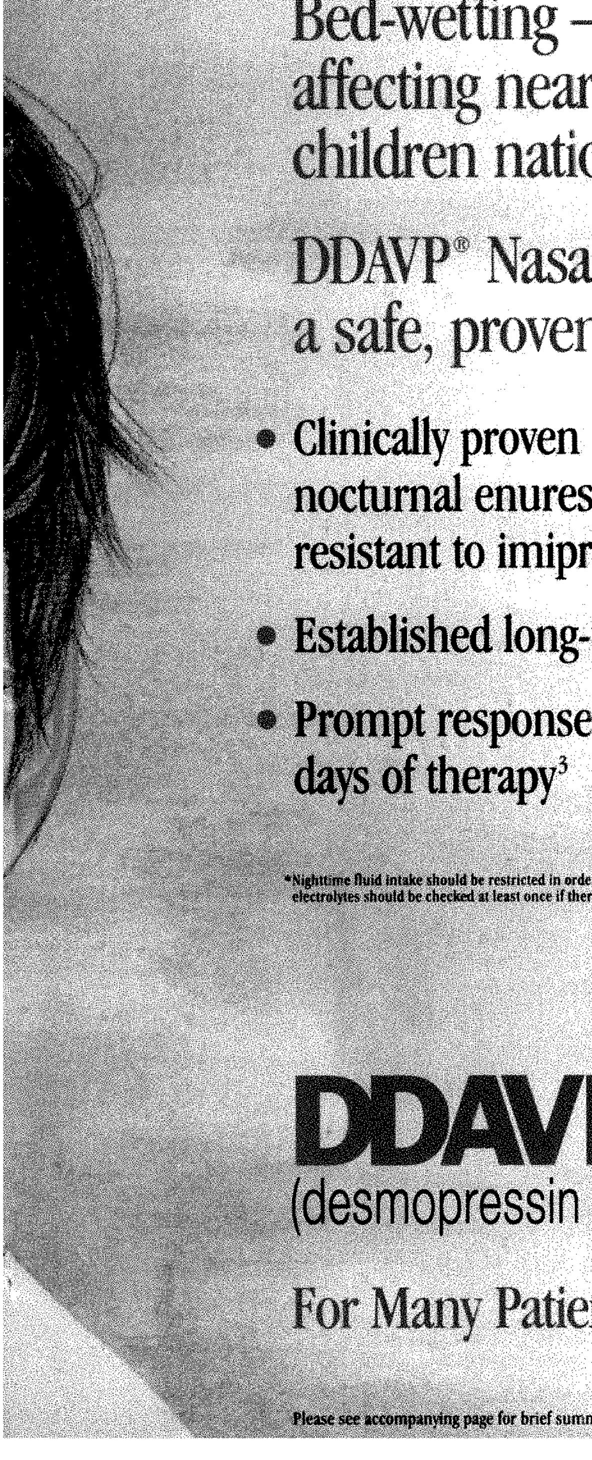

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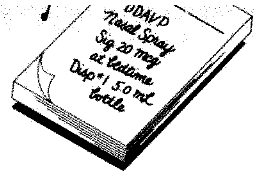

Brief Summary
CONTRAINDICATION: Known hypersensitivity to DDAVP Nasal Spray.
WARNINGS:
1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality and resulting seizures.
PRECAUTIONS:
General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.
DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.
Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used. For such situations, DDAVP injection should be considered.
Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP Nasal Spray should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.
Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.
Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities. No further information is available.
Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg.
Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.
Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.
Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nose-bleed, sore throat, cough and upper respiratory infections have also been reported.
The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	**PLACEBO (N=59)** %	**DDAVP 20 mcg (N=60)** %	**DDAVP 40 mcg (N=61)** %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see full prescribing information in product circular.

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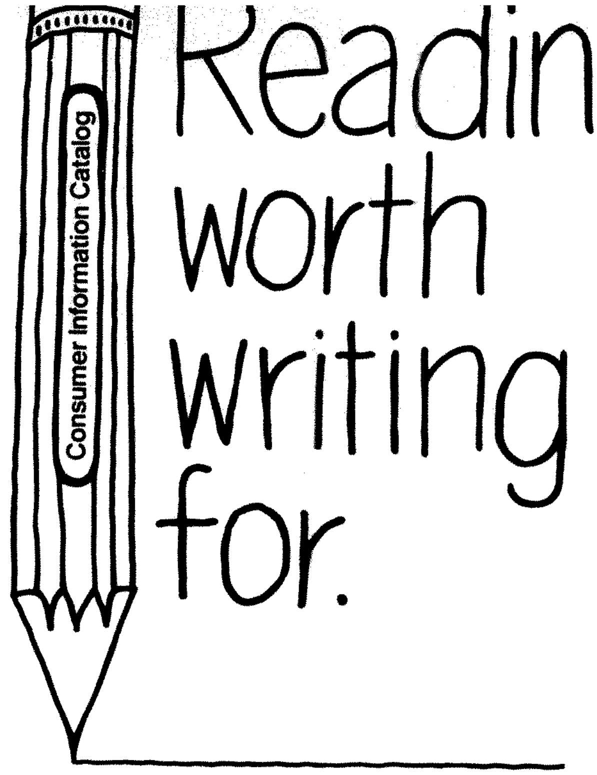

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Gun-Related Violence in and Around Inner-City Schools

Joseph F. Sheley, PhD; Zina T. McGee, MA; James D. Wright, PhD

• ***Objective.*** **—To assess the degree to which inner-city high school students are victimized by threat of or actual firearm attack.**

Design. **—Cross-sectional survey.**

Setting. **—Ten inner-city high schools in five cities in four states.**

Participants. **—A total of 1653 male and female inner-city high school students responding anonymously.**

Selection Procedures. **—Volunteer, convenience sample.**

Interventions. **—None.**

Measurements and Results. **—Twenty-three percent of respondents were classified as victims. Major variables predicting victimization levels were gender, number of siblings, exposure to violence outside of school, and personal violence-related attributes. Only one in 10 victimizations appeared to be random (ie, not predicted by these variables).**

Conclusions. **—Violence in school is brought into, rather than generated by, the school. Victimized students have characteristics that put them at higher risk of victimization than other students. Given the large number of victimizations and the large number of respondents with risk characteristics, intervention at the individual level seems ineffective. Instead, alteration of community social structure and culture appears to be the appropriate, although difficult, avenue of change for gun-related victimization levels.**

(*AJDC.* 1992;146:677-682)

Gun-related violence among high school youths increasingly commands the attention of the public health professions and has become a leading cause of morbidity and mortality among the young. High school–aged youths committed 7000 homicides with firearms between 1980 and 1989.[1] In 1989, 81% of the homicides of persons aged 15 to 19 years were accomplished with guns.[2] Homicide, most often committed with firearms, is now the leading cause of death of young black males.[3] Victimization survey data for 1989 indicate that 2% of the nation's students aged 12 to 19 years were victims of violent crime in or around their schools within the previous 6 months.[4]

Security has become a major difficulty for school administrators.[5] Of 11 000 eighth- and 10th-grade boys surveyed in 20 states in 1987, 3% reported having brought a handgun to school.[6] A study of 390 city high school students conducted in Baltimore, Md, in 1987 found that almost half of the boys had carried a gun at least once (*Newsweek.* January 11, 1988:18). Four percent of students in a nationally representative sample of students in grades 9 through 12 studied in 1990 reported carrying a firearm (though not necessarily in school) within the last 30 days. Twenty-one percent of the black males in the sample had carried a gun during the previous month.[1]

As enlightening as these figures are, they are too general to offer much direction for policy-making. First, they provide no information about the subpopulation of students seemingly most at risk for experiencing gun-related violence: those in inner-city high schools. What percentage of inner-city juveniles are victims of gun-related violence? Second, the research published to date reports only a few characteristics of the victims of school-related violence in general[4] and little or nothing about the victims of gun-related violence specifically. Knowledge of the characteristics of students most at risk for experiencing gun-related violence can be used to guide policy-making to reduce the risk for such violence.

Our study provides some of this information. We identified the amount of gun-related victimization, in schools and in transit to and from schools, for a sample of inner-city high school students from five US urban centers. We examined four general classes of predictors of gun-related victimization in students: (1) sociodemographic characteristics, (2) exposure to violence outside of school, (3) exposure to violence within the school, and (4) possible violence-engendering activities of the students themselves. Our aim in examining these variables was to determine whether policy designed to reduce the risk of gun-related violence among students was best directed at social and cultural institutions outside of schools or at practices and structures within schools.

Sociodemographic factors (age, race, and gender) are traditionally linked to victimization by violent crime and, especially, to victimization with handguns.[7,8] Exposure to violence outside of school implies that individuals are encouraged to behave violently. They may also be more likely to carry firearms for protection or for other reasons to be more ready to respond violently in a social world they see as hostile and dangerous.[9] A higher level of exposure to violence in school, with all else being equal, in-

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dicates a higher risk of victimization. Involvement in violence-related activities may heighten the risk for victimization. Carrying weapons, for example, raises the stakes in disputes that otherwise would have been settled less violently. Involvement in drugs (either as a user or seller) has also been linked to serious juvenile delinquency[10] and higher levels of victimization in schools in general,[4] and, thus, is a critical variable in this analysis.

METHODS

Sample

The analyses reported here are based on data derived from responses to self-administered surveys completed by 1653 students in 10 high schools in the United States in spring 1991. The schools in question were located in inner cities near state correctional facilities that were part of a related study. In all cases, local school administrators viewed the topic of gun possession and use by students as highly politically charged. They consented to our study only on the guarantee that their districts and schools would not be identified in the publication of our research results. Respecting their wishes, we note here only that we obtained responses from schools in large, prominent cities in California, Illinois, Louisiana, and New Jersey. Schools selected for study were identified by the administrators as typical inner-city schools that had experienced firearms incidents in the recent past and whose students likely encountered gun-related violence (as victims, perpetrators, or bystanders) out of school. Enrollments in these schools ranged from 900 to 2100.

The survey was introduced to students as a national study of firearms and violence among youths. Participation in the study was voluntary and anonymous. The percentage of student populations surveyed ranged from 7% to 21% (mean, 10%). The number of students surveyed per school averaged 165 (range, 109 to 229). In four of the 10 schools sampled, students were offered $5 to participate in the survey. Ultimately, neither financial inducement nor site more generally was tied to response variation across survey items. Owing primarily to respondent fatigue and varying reading skills, response rates differed by item. Average incompletion rate per survey item was 10%. The incompletion rate never exceeded 24%.

Table 1 offers a sociodemographic description of the high school students. The numbers of male and female respondents were roughly equal. Characteristic of inner-city high schools today, 75% of respondents were black; 16%, Hispanic; and only 2%, white. Most of the students were between 15 and 17 years old (mean age, 16 years). The modal grade level was 10th grade. Most respondents lived with both parents or with their mothers only. Twenty-five percent of the students had five or more siblings (mean number of siblings, 3.5). Nearly 80% of the respondents were unemployed.

Measurement

The dependent variable in this study, gun-related victimization, was measured by combining responses to survey items involving (*a*) threats with guns, and (*b*) being shot at while in school or in transit to or from school in the last few years. In either case, response categories range from "never" (scored as 0) to "many times" (scored as 3). Each response to the survey item regarding gun-firing was doubled to weight it as the more serious offense. Thus, respondents could have received a gun-related victimization score ranging from 0 (never threatened or shot at) to 12 (threatened "many times" and shot at "many times").

The measurement of the sociodemographic variables was straightforward (Table 1). For correlational and regression analyses, race first was recoded as a series of dummy variables and then dichotomized as "black/nonblack." Neither coding formula produced findings different from the other. Living arrangement was coded according to degree of habitation with parents—living with both (scored as 3), living with either parent (scored as 2), and living with neither parent (scored as 1).

Table 1.—Sociodemographic Characteristics of Inner-City High School Students

Characteristics	Males, % (n=765)	Females, % (n=829)	All Students, % (n=1594)
Gender	48	52	100
Age, y			
14	7	7	7
15	24	27	25
16	27	31	29
17	22	23	22
≥18	19	13	17
No. of students	753	829	**1582**
Race			
White	3	2	2
Black	72	78	75
Hispanic	19	13	16
Asian	5	4	5
Other	1	3	2
No. of students	756	829	**1585**
Grade			
9	25	25	25
10	32	33	33
11	21	23	21
12	22	19	21
No. of students	747	825	**1572**
Living arrangement			
With both parents	44	36	39
With mother only	36	45	41
With father only	5	4	5
With other relative	10	9	9
Other	5	6	5
No. of students	752	833	**1585**
No. of siblings			
0	5	4	4
1	14	14	15
2	21	23	22
3	20	18	19
4	14	16	15
≥5	26	25	25
No. of students	707	799	**1506**
Employment			
No	72	82	78
Yes, working less than 20 h/wk	14	9	11
Yes, working more than 20 h/wk	14	9	11
No. of students	746	825	**1571**

Exposure to violence outside of school was measured based on three items. First, respondents were asked how many males in their families carried guns habitually outside of the home. Second, they were asked the same question concerning their friends. For both items, response categories range from "none" (scored as 1) to "all" (scored as 4). Third, they were asked to what extent they strongly disagreed (scored as 1) or strongly agreed (scored as 4) that they lived in neighborhoods in which guns were plentiful and easily accessible.

Exposure to violence in school was measured in three ways. First, respondents were asked whether they agreed or disagreed with the statement that they felt scared most of the time at school. Second, they were asked whether they agreed that there was a lot of violence in their school. For both items, response categories ranged from "strongly disagree" (scored as 1) to "strongly agree" (scored as 4). Finally, respondents were asked how many students they personally knew who carried guns to school. Response categories ranged from "none" (scored as 0) to "almost all" (scored as 4).

Finally, personal violence-related activities were measured in terms of the extent to which respondents carried guns outside of school and on school property. Response categories for both items range from "never" (scored as 0) to "almost all the time" (scored as 4). Hard drug use was measured through combining responses concerning use of each of three drugs: heroin, cocaine, and crack. A respondent might have used each "never" (scored as 0) to "almost all the time" (scored as 4) in the year or two preceding administration of the survey. Combining the items produced scores ranging from 0 to 12 (used all three substances "almost all the time"). Finally, if respondents had dealt drugs (ie, been a dealer or worked for a dealer) they received a score of 1; if not, a score of 0.

RESULTS

Gun-Related Victimization

Twenty percent of the students had been threatened with a gun, and 12% had been shot at (Table 2). Twice as many males as females had been threatened with a gun, and three times as many males as females had been fired upon. Twenty-three percent of the sample had gun-related victimization scores of at least 1; 10% had scores exceeding 3. Again, males exceeded females in their combined gun-related victimization scores.

Table 2 also presents findings concerning the three independent variables in this study: exposure to violence outside of school, exposure to violence in school, and personal violence-related activity.

Exposure to Violence Outside of School

Males in the families of 39% of the respondents habitually carried guns outside of their homes. Thirty-five percent of the respondents had friends who routinely carried guns. Twenty-three percent of the respondents characterized their neighborhoods as replete with easily accessible guns. Females were slightly more likely than males to report males in their families carrying guns, although males were considerably more likely to have friends who carried guns. Perceived availability of guns in the neighborhood was roughly the same for both genders.

Exposure to Violence in School

Thirty-eight percent of students agreed that there was a lot of violence in their schools. Females were more likely to agree than males. Fifteen percent of the respondents (males and females alike) agreed that they were scared at school almost all of the time. Forty-six percent of respondents personally knew schoolmates who had carried guns to school during the last year. The value for males in this survey item was only 3 percentage points higher than for females.

Personal Violence-Related Behaviors

Twenty-two percent of the students carried a gun outside of school, and 6% carried a gun at school at least "now and then." Males were three times more likely than females to have engaged in each of these behaviors. Additionally, 4% of the students had used hard drugs during the last 2 years. Half of this subsample had drug use scores of five or more. Again, males were three times more likely than females to use hard drugs. Finally, 16% of respondents reported having dealt drugs; males' involvement in drug dealing exceeded that of females by 9 percentage points.

Table 2.—Gun Victimization, Exposure to Violence, and Personal Violence-Related Activity Among Inner-City High School Students*

Variable	Males, %	Females, %	All Students, %
Gun victimization			
Threatened with a gun	28 (n=655)	13 (n=733)	20 (n=1388)
Shot at with a gun	17 (n=647)	5 (n=733)	12 (n=1380)
Victimization score			
0	66	85	77
1	10	6	8
2	7	5	6
≥3	17	4	9
No. of students	592	732	**1324**
Exposure to violence outside of school			
Males in family carry guns			
No	63	58	61
Yes	37	42	39
No. of students	692	790	**1482**
Friends carry guns			
No	58	72	65
Yes	42	28	35
No. of students	684	784	**1468**
Access to guns in the neighborhood			
Strongly disagree/disagree	77	75	77
Strongly agree/agree	23	25	23
No. of students	630	764	**1394**
Exposure to violence in school			
Students carry guns to school			
No	52	55	54
Yes	48	45	46
No. of students	717	804	**1521**
A lot of violence in school			
Strongly disagree/disagree	65	59	62
Strongly agree/agree	35	41	38
No. of students	533	680	**1213**
Often feel afraid in school			
Strongly disagree/disagree	86	85	85
Strongly agree/agree	14	15	15
No. of students	537	682	**1219**
Personal violence related-activity			
Carry a gun outside of school			
No	65	89	78
Yes	35	11	22
No. of students	699	762	**1461**
Carry a gun to school			
No	91	97	94
Yes	9	3	6
No. of students	709	775	**1484**
Hard drug–use score			
0	93.4	97.9	95.8
1	1.0	.6	.7
2	1.0	.3	.6
3	0.3	None	0.2
4	0.5	None	0.3
≥5	3.8	1.2	2.4
No. of students	576	714	**1290**
Dealing drugs			
No	79	88	84
Yes	21	12	16
No. of students	567	718	**1285**

*Number of students indicates total number of students of each gender or total number of students of both genders for whom the given information was available.

Table 3.—Correlation Matrix of Sociodemographic Characteristics, Exposure to Violence, Personal Violence-Related Activity, and Gun Victimization Variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Gun-related victimization		.23*	.01	−.01	.06†	.01	.04	.26*	.21*	.15*	.19*	.10†	.02	.46*	.30*	.23*	.35†
2. Gender			.06†	.04	.01	.05†	.10*	.15*	−.05*	.06†	.03	−.06†	−.02	.28*	.12*	.09*	.13*
3. Age				−.04	.06†	−.08†	.23*	.04	−.01	.06†	.04	−.02	−.02	.05	.05†	.05	.03
4. Race					.06†	.09*	−.01	.06†	−.09†	−.07†	−.08†	−.01	.06†	−.01	−.01	.08†	−.04
5. Number of siblings						−.04	.05†	.04	.02†	.01	.05†	.08	.07†	.02	.03	.03	−.01
6. Parental living arrangement							−.02	.06†	.02	−.03	.02	.02	−.02	.06†	.01	−.02	−.01
7. Job status								.04	−.01	.05	.10*	−.03	−.03	.10*	.01	−.01	.07†
8. Friends carrying guns									.33*	.29*	.29*	.18*	.09†	.36*	.22*	.15*	.33*
9. Male relatives carrying guns										.21*	.24*	.06†	.03	.23*	.15*	.12*	.21*
10. Guns in neighborhood											.25*	.25*	.13*	.18*	.14*	.09†	.24*
11. Kids in school with guns												.16*	.04	.27*	.20*	.07†	.01
12. Violence in school													.38*	.10†	.13*	.06†	.12*
13. Afraid in school														−.02	.01	.04†	.01
14. Carrying a gun															.43*	.21*	.43*
15. Carrying a gun in school																.21*	.26*
16. Using hard drugs																	.23*
17. Drug dealing																	

*$P<.001$.
†$P<.05$.

Intercorrelations

Table 3 presents correlations among the variables examined in this study. Only two sociodemographic characteristics, gender and number of siblings, were related at the zero-order level to gun-related victimization scores. All remaining variables (except feeling scared at school) were linked to gun-related victimization. However, the coefficients in the table indicate modest interrelations among the independent variables. To ascertain which variables predicted gun-related victimization outside of the influence of the other variables, we entered all variables into regression equations. The findings presented in Table 4 reflect the model after eliminating the variables that were not associated with gun-related victimization and that, when eliminated, would not affect the adjusted explained variance.

With the exception of gender and number of siblings, none of the sociodemographic variables or survey items examining exposure to violence in school was ultimately linked to gun-related victimization score. That is, age, race, living situation, employment situation, and grade level at school did not influence gun-related victimization when examined alone and disregarding influence from other variables. This was also true for level of exposure to violence in school (amount of violence in school, feeling scared in school, and the number of persons known by the respondent to have carried guns to school).

Gun-related violence that occurs in and around inner city schools derives mainly from factors external to the schools themselves. Males and children from large families were more at risk for gun-related victimization than were females and children from smaller families. Beyond these factors, the variables associated with victimization involved exposure to violence outside of school and personal violence–related behaviors. The victims of gun-related violence in school or in transit to or from school were youths from families in which males carried guns routinely, youths who carried guns themselves (either in or out of school), and youths who used or sold drugs.

Table 4.—Regression Estimates of the Influence of Sociodemographic Characteristics, Exposure to Violence, and Personal Violence-Related Activity on Gun-Related Victimization*

Independent Variables	b	β
Gender	.391	.119†
No. of siblings	.046	.079‡
Males in family carry guns	.241	.073‡
Student carries a gun outside of school	1.246	.301†
Student carries a gun in school	.684	.089‡
Using hard drugs	.139	.103‡
Dealing drugs	.576	.130†
Constant	−.1338	Not applicable

*$n=1049$. $R^2=.29$; adjusted $R^2=.28$; $F=59.4825$ ($P<.001$).
†$P<.001$.
‡$P<.05$.

Random vs Nonrandom Victimization

Many discussions of violence in and around schools depict the problem as essentially random, a matter of youths being in the wrong place at the wrong time. While some victims are no doubt stricken randomly, our findings indicate that most decidedly are *not*. Indeed, of the 322 victims of gun-related violence in this study, 76% had at least one of the five nondemographic characteristics linked to victimization in Table 4; 90% of respondents with victimization scores of 3 or more had at least one such attribute.

To clarify further the risk factors for gun-related victimization, we sorted out the 77 respondents who had experienced victimization but who did *not* display any of the previously described characteristics. In this subgroup, gender was still important; beyond that, the only significant variable was the number of persons the respondent knew personally who carried guns in school. Thus, with no other risk factors present, simply knowing people who carried guns to school put one at risk for victimization. Fifty-two percent of the 77 victims knew someone who had carried a firearm to school. The exact nature of this relationship was not wholly clear. If it was a matter simply of knowing identities, the variable might reflect a risk factor of the school environment per se. However, because none of the other measures of school environment was related to victimization scores, we suspect that this variable, too, was largely behavioral; it more likely indexed the tendency of the respondent to affiliate with people who carry guns to school. If this is the correct interpretation, only 37 of the 322 victims examined lacked any apparent nondemographic attribute placing them at risk. Perhaps one gun-related victimization in 10 is the result of a youth being "in the wrong place at the wrong time." The remaining nine out of 10 result either from behavioral risk factors (eg, carrying guns, being involved with drugs, or affiliating with people who carry guns) or from environmental risk factors that exist *outside* of the schools themselves.

COMMENT

We have sought in this study to assess the degree to which inner-city high school students are victimized by the threat of or by actual gun-related violence and to ascertain the associated risk factors. Our findings indicate that gun-related victimization among inner-city school youths far exceeds that of students nationally. Whereas 2% of the nation's students report being victims of some form of violence (albeit for only 6 months[4]), 23% of inner-city students in our sample had been victims, during the last few years, of gun-related violence specifically. Males, especially, had high victimization rates (one in three males in our sample). Aside from the significant influence of gender and number of siblings, major predictors of gun-related victimization in school or in transit to or from school involved whether or not family members carried guns, the extent to which students themselves carried guns in and out of school, whether or not students used and sold drugs and, for those with none of these characteristics, whether they affiliated with others who carried guns to school. In the final analysis, 89% of the victims in this study had at least one characteristic that put them at greater risk for gun-related victimization. Gun-related victimization of youths does not "just happen"; rather, it is patterned violence.

Our results suggest that schools themselves do not generate gun-related violence as much as they represent the location where violence spawned outside of the institution is played out. Most gun-related violence that occurs in schools or on the way to and from schools occurs because many students come from social milieus where carrying and using guns is commonplace, because some pupils engage in behaviors known to breed violence (eg, drug trafficking), or simply because carrying guns (or affiliating with those who do) promotes more consequential outcomes in otherwise "normal" school-yard disputes. Apparently, only one in 10 victims (not a trivial figure in that it constitutes 2% of our entire sample of inner-city students) is involved in random gun-related violence. These, we assume, are students who become embroiled in disputes situationally rather than through higher-risk attributes or who are the random targets of robberies or the victims of gunfire meant for someone else.

Increased security in and around schools may or may not reduce levels of gun-related victimization.[6] All 10 schools in our study had histories of problems with guns and had already implemented rather tight security measures when our data were collected. Likewise, little difference has been found in rates of violent victimization between schools with and without conventional security measures such as patrolled hallways and visitor check-ins.[4] A broader policy initiative, more epidemiologic in nature, would involve some form of direct intervention in the lives of youth at risk for school-related violence.[11] However, because the predictive variables that surfaced in this analysis were either broad sociodemographic characteristics (gender and number of siblings), illegal behaviors (such as involvement in drugs), or behaviors that are not obvious before the fact (such as carrying guns or affiliating with those who do), the ability to identify those at risk before they engage in or are victims of violence is seriously limited.

Our findings point *away* from intervention at the individual level and *toward* changes in the larger familial, communal, and social situation of those most involved in gun-related violence. Inner-city youths obviously do not assume new social identities as they pass through school gates; likewise, the schools are obviously not immune to the many problems of the communities in which they are located. As we have seen, violence in and around schools is *not* predicted by factors inherent in the school environments themselves; rather, violence spills into the schools from the world outside. Given the concentration of so much of this violence (and other social ills) among inner-city inhabitants—and, by this study's account, among such high proportions of those inhabitants—structural and cultural remedies command attention.

Structurally, we are experiencing the development of an inner-city underclass unlike any in our past. In a shrinking industrial economy, we are witnessing the disintegration of the traditional family, increasing poverty and homelessness, diminishing health, and deteriorating educational institutions. The desperation of this situation is enhanced by the apparent enormity of the drug problem and the ready availability of firearms to all. Given all this, perhaps the surprising result is not that there is so much violence in the inner city, but that there is so little.

These structural ingredients have fostered a culture of violence that, unfortunately, may survive even after the structural situation has improved. Inner-city youths know they are at risk for violent victimization, and they are now accustomed to arming themselves for protection (from violence in general or from violence associated with illegal activities). They have been introduced to sophisticated weapons, including the automatic and semi-automatic firearms that currently occupy the media's attention. Even were structural elements to improve, the perceived need for protection would not disappear rapidly. Nor is it likely that, as conditions improve, youths will begin using less lethal weapons. Guns have become a part of the culture of inner city, underclass youths. As a cultural element, the desire to carry firearms will last long beyond the need to carry firearms (even assuming, perhaps unrealistically, that the need itself would be reduced by structural improvements).

It is clear that the problem of violence in inner city schools cannot be isolated from the problem of violence in larger society; violent neighborhoods and violent communities will produce violent schools whatever measures the schools themselves adopt. It is equally clear that this "larger" problem will not yield to simplistic, unicausal solutions. In this connection, it is useful to point out that nearly everything that leads to gun-related violence among youths is already against the law. What is needed are not new and more stringent gun laws but rather a concerted effort to rebuild the social structure of inner cities.

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BOOK REVIEW

Practical Statistics for Medical Research

By Douglas G. Altman, 400 pp, $75 (hardcover)/$37.50 (paperback), New York, NY, Chapman & Hall Ltd, 1991.

In 1980, the *British Medical Journal* (volume 281) published a series of readable and informative articles by Douglas G. Altman entitled "Statistics and Ethics in Medical Research." Now comes a monograph by the same author, and it is a winner. Health care professionals recognize their obligation to have some familiarity with biometry, biostatistics, clinical epidemiology, or whatever the subject might be called. We all need to understand at least some of the fundamental ideas and methods if we expect to follow the current biomedical literature. Researchers must know considerably more than just the fundamentals.

Textbooks of biostatistics are commonly frustrating to the clinician or biomedical researcher who has not had formal training in statistics. The books tend to use strange, often idiosyncratic, notation. The algebra may be arcane or cryptic. The technical discourse is often too esoteric for even the most diligent reader of medical literature.

Altman's excellent book avoids these barriers to understanding. The text is comfortably fluent; it describes and explains without jargon or obscurities. The mathematic segments are clearly presented and should be accessible to any college graduate. The author describes the ideas associated with various methods without forcing the detailed algebra of the analyses. Particularly attractive are the discussions of newer procedures such as multivariate methods, logistic regression, and survival models. There is also a helpful, nontechnical chapter on using a computer. The examples use actual biomedical data, rather than invented sets of values. (We can forgive a reference to the present journal as *"Am J Dis Chest."*)

Altman is the head of the Medical Statistics Laboratory, Imperial Cancer Research Fund, London, England. He has provided health care professionals with a remarkably instructive, accessible, and useful guidebook. Although I have not conducted an exhaustive survey of textbooks in this field, this is the most impressive monograph on medical statistics that I have read. It is no longer necessary to be intimidated by biostatistics.

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Gangs, Drugs, and Homicide in Los Angeles

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• *Objective.*—To assess the theory that youth homicides in Los Angeles, Calif, are largely attributable to gang involvement in the trafficking or use of drugs.

***Design, Setting, and Participants.*—First, we analyzed all homicides in a police database that occurred in Los Angeles between January 1, 1986, and August 31, 1988, to examine the association between gang activity and narcotic use and trafficking. Second, we used detailed data from police files to examine the same associations for a subset of homicides in south central Los Angeles. Third, we investigated the association between gang homicide victimization and victim cocaine use for all 1987 Los Angeles homicides. Finally, we compared narcotics arrest histories for gang homicide victims with histories for other homicide victims.**

***Results.*—Gang-motivated homicides were less likely than other homicides to involve narcotics, and narcotics-motivated homicides were less likely to involve a gang member. Victims of gang-motivated homicides in 1987 were less likely than other homicide victims to have detectable levels of blood cocaine. Finally, young victims of gang-involved homicide were no more likely to have a history of narcotics arrests than other victims.**

***Conclusions.*—Our investigation does not support the theory that a substantial proportion of homicides are attributable to gang involvement in narcotics trafficking.**

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Between 1980 and 1988, the homicide rate in Los Angeles, Calif, was more than double the rate for the state of California (unpublished data, Los Angeles Police Department [LAPD] and the California Department of Health Services, 1989). According to the gang investigation unit of the LAPD, gang-related homicides constitute an increasingly large proportion of all homicides in Los Angeles. In 1983, 14.8% of all homicides were gang-related compared with 25.2% in 1987.

There is also objective evidence that cocaine abuse and trafficking have increased in Los Angeles. Both the number of medical encounters for problems related to cocaine abuse and cocaine seizures by law enforcement agencies have increased.[1] Furthermore, in 1987, cocaine or cocaine metabolites were detected in the blood of more than one of every five homicide victims in Los Angeles County at the time of death.[2]

Both gang activities and narcotics trafficking are inherently violent activities that are independently associated with an increased risk of homicide perpetration and victimization.[3] However, a prevalent theory in Los Angeles in the late 1980s was that a substantial proportion of the increasing incidence of homicide among the youth in that city was attributable to the increasing involvement of gang members in illicit drug trafficking, drug use, or both. According to this theory, the involvement of gangs in the narcotics trade is a particularly explosive mix, resulting in increases in violence far beyond what might be expected from the sum of the independent contributions of gang activity and narcotics trafficking. The general acceptance of this theory is reflected in both the popular media (*Los Angeles Herald Examiner.* January 14, 1989:A4; *Rolling Stone.* September 22, 1988:64-72, 114-116) and in official reports, such as the 1988 report from the California Council on Criminal Justice Task Force on Gangs and Drugs.[4] The hypothesized interaction of gangs and narcotics in causing homicide is generally thought to involve narcotics trafficking, particularly cocaine trafficking. It is also conceivable, however, that increasing *use* of narcotics by gang members could contribute to higher homicide rates, either because of direct pharmacologic effects of narcotics that promote violent behavior or because of the need of narcotics users to commit violent crimes to supply their addictions.[5]

Despite its popularity, there is little evidence to support the theory that gang involvement in the narcotics trade is responsible for a substantial proportion of homicide among youth in Los Angeles. This issue should be critically examined because it has direct relevance to the design of homicide prevention programs. If a large proportion of homicides are attributable to this intersection of gang activity and narcotics trafficking (or use), then increased efforts to prevent gangs from selling (or using) narcotics might be the most effective short-term strategy for reducing the death toll from homicide in Los Angeles. If, on the other hand, narcotics trafficking and gang activity are more important as independent contributors to homicide than as cofactors, a prevention strategy tar-

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geted primarily at the intersection of these two inherently violent activities would be misdirected.

Unfortunately, no single data source is sufficient for a comprehensive examination of the various possible relationships between gangs, narcotics, and homicide. Police files, vital statistics, and medical examiner's data files provide relevant information, but each data source has limitations that prevent a straightforward epidemiologic investigation. As part of an investigation of homicides in Los Angeles, however, we were able to make use of several distinct but complementary data sources, each of which provided some evidence about the hypothesized association between gang activity, narcotics use or trafficking, and homicide.

MATERIALS AND METHODS

The available data sources permitted us to evaluate the following four hypotheses: (1) homicides due to gang rivalry (gang-motivated homicides) are more likely than others to involve narcotics; (2) homicides resulting from conflicts related to narcotics trafficking (narcotics-motivated homicides) are more likely than others to involve gang members; (3) victims of gang-motivated homicides are more likely than others to have been using cocaine before death; and (4) victims of homicides involving a gang member (gang-involved homicides) are more likely to have a history of arrests related to narcotics (possession or distribution) than are victims of homicides that involved neither gangs nor narcotics.

Each of these hypotheses posits possible associations between narcotics trafficking or use and gang involvement in homicides in Los Angeles. Because street gang members are mostly younger than 25 years, our analysis emphasizes youth homicides.

Narcotics and Gang Involvement in Homicides

We used two separate data sources to examine the first two hypotheses. The first is a database maintained by the homicide unit of the LAPD primarily for investigative purposes, which we refer to as the *LAPD database* (Table 1).

It contains information on homicide victim demographics, crime circumstances, motives, weapons, and suspects, as well as a brief summary of the incident. Information on homicides is entered by detectives at the outset of an investigation and is updated periodically. Motive was entered by the detective as a word or short phrase ("gang," "gang fight," "domestic," "narco dispute," etc). Motive was then counted by us as "narcotics-motivated" if narcotics appeared in the description of motive, "gang-motivated" if gang appeared in the description, or "motivated by one of a variety of other factors." Apart from the primary motive, "narcotics involvement" and "gang involvement" were entered by the police as separate variables. By definition, all narcotics-motivated homicides were "narcotics-involved," and all gang-motivated homicides were "gang-involved."

The LAPD defines a gang as "a group of persons working to an unlawful or antisocial end" (from LAPD intradepartmental correspondence). Operationally, gang membership is ascertained by detectives entering the data, based on whether the subject is listed in the computerized gang roster of the LAPD or based on characteristics of the event, including use of known hand signals used by gangs, gang-specific clothing, and witness statements.[3]

We verified the completeness of this database by manually comparing homicides in it with those in the master crime file housed in the LAPD data unit's mainframe computer. For the period of study, 97% of the homicides in the master file were also found in the LAPD investigative database. The determination of gang motive by the LAPD had previously been validated.[6] Further, an independent gang unit of the LAPD examined each 1988 homicide to ascertain whether it was gang-motivated. Of the 82 homicides determined to be gang-motivated by the unit, 64 (78%) were described as having a gang motive in the LAPD database. Of the 416 homicides not ascertained to be gang-motivated by the gang investigation unit, 385 (93%) were also described as other than gang-motivated in the LAPD database.

Table 1.—Study Questions and Data Sources

Question No.	Study Questions	Data Sources Used
1	Are gang-motivated homicides more likely than other homicides to involve narcotics?	LAPD database,* SCLA investigative files†
2	Are narcotics-motivated homicides more likely than other homicides to involve gangs?	LAPD database,* SCLA investigative files†
3	Are victims in gang-motivated homicides more likely than other homicide victims to have been using cocaine?	LAPD database linked with LA County Coroner's data‡
4	Are victims of gang-involved homicides more likely to have a narcotics-related arrest than are victims of homicides that were neither gang nor narcotics involved?	LAPD database (sample),§ LAPD arrest records

*Based on information from the Los Angeles Police Department (LAPD) database, 2162 homicide victims between January 1986 and August 1988 were aged 10 years or older.

†Based on south central Los Angeles (SCLA) investigative files, 114 homicide victims were aged between 10 and 19 years.

‡Based on blood cocaine levels of 74% of 618 homicide victims in the LAPD database in 1987.

§Randomly selected homicide victims in south central Los Angeles aged 15 to 24 years between January 1986 and August 1988 included 31 cases (gang-involved homicides) and 36 controls (neither gang- nor narcotics-involved homicides).

We determined that data had been reliably entered into the LAPD database for the period of January 1, 1986, through August 31, 1988. We therefore analyzed data on the victims of all homicides that occurred in Los Angeles during this period, excluding homicides due to legal intervention (during the interruption of a crime). We constructed a set of contingency tables to compare the frequency of gang involvement in narcotics-motivated homicides with that in other homicides. We also constructed contingency tables to compare the frequency of narcotics involvement in gang-motivated homicides with that in other homicides. In our analysis, we stratified the victims into two age groups: 10 to 24 years old, and 25 years and older.

Our second data source was the investigative homicide files kept in police district offices. Of 18 police districts in the city, the police had identified four contiguous districts as having the highest concentration of youths involved in gangs and homicides involving gangs. We refer to this area as *south central Los Angeles*. District office files for each homicide contain initial investigative reports and summary follow-up reports. We limited the case subjects in this analysis to a subset of the population that we studied using the LAPD database: homicide victims aged 10 to 19 years who died in south central Los Angeles from January 1, 1987, through August 31, 1988 (Table 1). We extracted demographic data, information on the weapons used, motive, relationship of victim to offender, whether narcotics were involved, and various incident characteristics.

For this part of the analysis, we defined a gang-involved homicide as one in which either the victim or perpetrator was identified as a gang member through the evidence collected. We defined a gang-motivated homicide as one that resulted from violence between rival gang factions. We defined a narcotics-involved homicide as one in which narcotics were found at the scene of the homicide or on the body of the victim or perpetrator, or in which evidence indicated that narcotic sales or use was occurring at or near the time of the homicide. Finally, we defined a narcotics-motivated homicide as one that resulted from a violent conflict over a narcotics transaction. As with the LAPD database, we used these data to look at the levels of involvement of gangs and narcotics in narcotics-motivated and gang-motivated homicides, respectively.

Cocaine Use by Homicide Victims

To examine the third hypothesis, we supplemented data contained in the LAPD database with records from the Los Angeles County Coroner's Office for 1987. The Los Angeles County Coroner's Office analyzes blood specimens from all homicide victims in Los Angeles County for the presence of cocaine and a cocaine metabolite (benzoylecgonine) according to methods described elsewhere.[2] Detection of either compound was considered evidence of recent cocaine use. Complete data were available for homicides in 1987, and we were able to link the databases from the LAPD and the Coroner's Office for 74% of the homicides that occurred in Los Angeles in 1987 (Table 1). Homicide cases that could not be linked to data from the Coroner's Office did not differ substantially from those that could in terms of the victim's age, sex, or race, the police division in which the homicide occurred, or the perpetrator's motives. The most common reason for a failed linkage was inability to match records by the common identification number.

We examined the hypothesized association between recent cocaine use and being a victim of a gang-motivated homicide by comparing the frequency of positive cocaine levels in the blood of victims of gang-motivated homicide with those in victims of homicides not motivated by gangs.

Past Narcotics Arrests Among Homicide Victims

We tested our fourth hypothesis using a case-control study design. We defined case subjects as victims of gang-involved homicides and control subjects as victims of homicides that were neither gang- nor narcotics-involved. We evaluated the prevalence of history of narcotics arrest among cases compared with controls.

We randomly selected 36 case and 36 control victims of homicide from the LAPD database of ages 15 to 24 years who resided in one of the census tracts within south central Los Angeles and were killed between January 1, 1987, and August 31, 1988 (Table 1). Correct addresses were not available for five of the sampled gang-involved homicide victims, leaving 31 case and 36 control subjects.

We assessed the decedent's history of narcotics arrests using data from computerized county arrest records. After obtaining court permission, we searched computerized law enforcement databases using the decedent's name, address, and date of birth. Any arrest history was noted, including any history of narcotics arrests (for possession or for selling). We found that 42 of the 67 study victims had arrest records. We assumed that the absence of an arrest record was indicative of a victim having no arrests for any offense. We also assumed that the possibility that a record was not found because of an incorrect name or other clerical error was equally likely for case and control subjects.

Statistical Methods

Statistical testing was done using either the Mantel-Hantzel χ^2 test or a two-tailed Fisher's exact test. Odds ratios and 95% confidence intervals (obtained from Cornfield's approximation) were calculated with Epiinfo software (Centers for Disease Control, Atlanta, Ga).

Table 2.—Narcotics Involvement in Gang-Motivated Homicides in Los Angeles from January 1986 Through August 1988

Victims	Gang Motivated	Other Motive	
10 to 24 y old			
Narcotics involved	11	135	$P<10^{-7}$
Narcotics not involved	259	375	
Total	**270**	**510**	**780**
25 y and older			
Narcotics involved	7	281	$P<.05$
Narcotics not involved	68	1026	
Total	**75**	**1307**	**1382**
Total 10 y and older			
Narcotics involved	18	416	$P<10^{-7}$
Narcotics not involved	327	1401	
Total	**345**	**1817**	**2162**

RESULTS

Narcotics Involvement in Gang-Motivated Homicides

The LAPD database contained data on 2162 homicides that occurred between January 1, 1986, and August 31, 1988. Overall, it was noted that 18 (5%) of 345 gang-motivated homicides involved narcotics, whereas 416 (23%) of 1817 other homicides involved narcotics ($P \ll .01$; Table 2). For both younger and older homicide victims, gang-motivated homicides were significantly less likely to have involved narcotics than were other homicides.

Since all the narcotics-motivated homicides (conflict due to narcotics trafficking) are by definition in the "other" (comparison) homicide group when gang-motivated homicides are being examined, and since narcotics-motivated homicides are always narcotics-involved, there is an intrinsic bias toward finding more narcotics involvement in the "other" homicide group than in the gang-motivated homicide group. To account for this bias, we compared the frequency of narcotics involvement in gang-motivated homicides with that for homicides that were neither gang- nor narcotics-motivated. Gang-motivated homicides were still less likely to have involved narcotics than were other homicides. This finding held for all ages combined ($P<.005$) and for victims aged 10 to 24 years ($P<.001$). For victims 25 years and older, homicides that were gang-motivated were just as likely to involve narcotics as were homicides that were neither gang- nor narcotics-motivated (difference is not significant).

We obtained similar results from our detailed examination of investigation files for homicides among adolescents that occurred in south central Los Angeles. During the 20-month period from January 1, 1987, through August 31, 1988, there were 116 homicides in south central Los Angeles involving victims aged 10 to 19 years. We reviewed the investigative files of 114 of these homicides (records for two homicides were not available) and found that none of the 40 gang-motivated homicides involved narcotics.

Gang Involvement in Narcotics-Motivated Homicides

Overall, narcotics-motivated homicides were less likely than other homicides to have involved gangs (Table 3). Of the 281 narcotics-motivated homicides in the LAPD database, 30 (11%) were also noted to have involved gangs. Of the 1881 other homicides, 442 (23%) involved gang mem-

Table 3.—Gang Involvement in Narcotics-Motivated Homicides in Los Angeles From January 1986 Through August 1988

Victims	Narcotics Motivated	Other Motive	
10 to 24 y old			
Gangs involved	16	324	$P<10^{-7}$
Gangs not involved	81	359	
Total	**97**	**683**	**780**
25 y and older			
Gangs involved	14	118	$P=.3$
Gangs not involved	171	1078	
Total	**185**	**1196**	**1381***
Total 10 y and older			
Gangs involved	30	442	$P<10^{-5}$
Gangs not involved	251	1439	
Total	**281**	**1881**	**2162**

*Information for gang involvement was not available for one case.

Table 4.—Detection of Cocaine or Cocaine Metabolite in the Blood of Homicide Victims in Los Angeles in 1987

Victims	Gang Motivated	Other Motive	
10 to 24 y old			
Cocaine present	4	36	$P<.0005$
Cocaine not present	78	110	
25 y and older			
Cocaine present	8	119	$P=.7$
Cocaine not present	14	249	
Total 10 y and older			
Cocaine present	12	155	$P<.0001$
Cocaine not present	92	359	

Table 5.—Comparison of Narcotics Arrest Histories for Homicide Victims Between Ages 15 and 24 Years in South Central Los Angeles From January 1987 Through August 1988

Narcotic Arrest History	Homicides Involving Gangs	Homicides Involving Neither Gangs Nor Narcotics	Odds Ratio (95% Confidence Interval)
History of arrest	8	9	1.0 (0.3-3.6)
No history of arrest	23	27	

bers ($P \ll .01$). When the victims were stratified by age, this negative association between narcotics-motivated homicides and gang involvement was found only for those homicides involving victims younger than 25 years. The most common motive for homicides involving gang members was a gang conflict.

Since gang-motivated homicides (involving gang conflict) are always gang-involved (include a gang member as victim or perpetrator), and since gang-motivated homicides are by definition included in the comparison group in the preceding analysis, the negative association we found between narcotics-motivated homicides and gang involvement could theoretically be due to an artifactual bias. We therefore also compared gang involvement in narcotics-motivated homicides with gang involvement in homicides that were neither gang- nor narcotics-motivated. Still, narcotics-motivated homicides were less likely to have involved gangs than were homicides that were neither gang- nor narcotics-motivated for all ages combined ($P<.05$) and for victims 25 years or older ($P=.05$). For victims aged 10 to 24 years, narcotics-motivated homicides were no more or less likely to involve gangs than were homicides that were neither gang- nor narcotics-motivated (difference is not significant).

Of the 114 homicides in south central Los Angeles for which we reviewed actual investigative files, three were found to be narcotics-motivated. None of those three homicides involved gang members.

Cocaine Use by Homicide Victims

Victims of gang-motivated homicides in 1987 were significantly less likely than victims of other homicides to have cocaine or cocaine metabolites in their bloodstreams ($P<.0001$; Table 4). This negative association between being a victim of a gang-motivated homicide and recent cocaine use was found only for homicides involving victims between 10 and 24 years old ($P<.0005$). Among those 25 years and older, no such association was found.

Past Arrest Histories of Homicide Victims

Eight (26%) of 31 victims of gang-involved homicides had a history of narcotics arrests, whereas nine (25%) of 36 control homicide victims had a history of narcotics arrests (Table 5). Thus, victims of gang-involved homicides were no more likely to have a history of narcotics arrests than were victims of homicides that were neither gang- nor narcotics-involved (odds ratio, 1.0; 95% confidence interval, 0.30 to 3.6).

COMMENT

There is no question that a substantial proportion of homicides in urban America are attributable to gang activity and to narcotics trafficking In Los Angeles during the period studied, 16% of the homicides among persons aged 10 years and older were gang-motivated, and 13% were narcotics-motivated (Tables 2 and 3). Thus, three out of every 10 homicide victims died from violence between rival gang factions or from violence associated with narcotics trafficking. The results of our investigation, however, do not support the popular theory that a substantial proportion of homicides are attributable to gang involvement in narcotics trafficking. Indeed, our analysis of available data sources suggests that gang-motivated homicides do not tend to involve narcotics trafficking (or victim drug use), and narcotics-motivated homicides do not tend to involve gangs.

Past research on the relationship between gangs, narcotics trafficking, and violence is inconclusive.[7] In contrast to our findings, for example, Skolnick and colleagues[8] concluded (based on a series of interviews in California with inmates of correctional institutions and police and correctional officers) that street drug dealing in California is dominated by Black gangs organized specifically for the purpose of distributing crack cocaine (institutional gangs). Such gangs are said to be distinct from the more traditional neighborhood or cultural gangs. Klein and Maxson,[3] however, have suggested that it may be tautological to define gangs in terms of the common criminal activity that brings the members together as with institutional cocaine distributing gangs. It is quite possible that violence involving traditional youth street gangs that are loosely tied together by neighborhood allegiance is a phenomenon distinct from violence involving more highly organized institutional gangs or networks that exist for the purpose of marketing narcotics.

The hypothesis that the increasing rates of gang-related homicide result from an increasing gang involvement in narcotics trafficking presupposes that gang involvement in narcotics trafficking has actually increased. There is evidence, however, that this is not the case. A 1988 study by Klein et al[9] did not show a relationship between the dramatic increase in crack cocaine sales in Los Angeles during 1983 to 1985 and gang involvement in cocaine distribution. Fagan[10] interviewed 151 gang members younger than 21 years from three inner-city, high-crime neighborhoods, including south central Los Angeles. He concluded that illicit drug use and violence were widespread among gangs but that serious drug use and dealing by individual gang members occurred regardless of the prevalence of drug dealing within the individual's particular gang. He also concluded that drug use and sales by gang members did not necessarily increase the frequency or severity of violent behavior.

Each of the four data sources we used in our analysis has certain limitations. We were concerned, for instance, that in an atmosphere of heightened concern about gang violence there might be a bias in the LAPD database toward coding homicides involving gang members as gang-motivated or gang-involved without noting the roles of narcotics or other factors. It is also possible that police may purposely downplay the role of narcotics in a homicide to avoid the introduction of mental impairment as a defense in court proceedings. Our own review of police investigation files for a subset of homicides (those occurring in south central Los Angeles and involving victims aged 11 to 19 years) helps validate the data obtained from the LAPD database; however, since the findings were similar, we cannot completely rule out such misclassification bias. We compared gang classification within the LAPD database with an independent classification provided by the gang investigation unit of the LAPD and found reasonably good agreement, and past research has provided evidence of the validity of gang involvement in homicides by the LAPD.[6] Thus, misclassification bias of gang status is unlikely. In the future, researchers who evaluate existing police data may benefit from using court records or other sources of information to check further for misclassification bias.

We were able to obtain whole blood cocaine levels on a large, representative sample of homicide victims for 1987. The hypothesized association between illicit drug use and participation in violence would clearly be better tested by using data on drug use by all crime participants, including perpetrators. Unfortunately, existing data sources did not permit us to analyze the drug use of perpetrators.

Our finding that little or no association existed between narcotics-related arrests and gang-motivated homicide victimization further supports our conclusion that gang conflicts that result in a homicide are often independent of narcotics use and trafficking. Two limitations to this part of the analysis should be noted, however. First, we used the victims' history of narcotics arrests as a marker for their involvement in narcotics use or trafficking, and an arrest history may be an insensitive measure of such involvement. Second, the power of our analysis to detect a difference is limited by the small number of homicides that we studied. A separate, larger-scale study would be useful for confirming or refuting our findings.

Despite these limitations, we believe that the consistency of our findings across these different data sets strongly suggests that if gang activity and narcotics trafficking (or use) do interact to increase the risk of homicide, this interaction does not account for a large proportion of homicides (ie, the attributable risk percent is small). In light of this, we recommend that gang activity and narcotics trafficking or use be addressed as separate, important risk factors for homicide rather than as interrelated cofactors.

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The Diagnosis of Child Sexual Abuse

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• *Objective.*—**To examine how the history, psychological evaluation, medical examination, and child's response to the examination contributed to a diagnosis of child sexual abuse by an interdisciplinary team.**

Design.—**Patient series.**

Setting.—**Subspecialty clinic for evaluating prepubertal children alleged to have been sexually abused.**

Participants.—**One hundred thirty-two children alleged to have been sexually abused and their parents or guardian, evaluated consecutively in a subspecialty clinic between September 1989 and June 1990.**

Measurements/Main Results.—**A social worker interviewed the parents, a psychologist interviewed the child, and a pediatrician obtained a medical history and examined the child. Parents completed a Child Behavior Check list and the child's response to the physical examination was noted. Both a disclosure by the child and abnormal physical findings were significantly and independently associated with the team's diagnosis of sexual abuse, whereas the presence of sexualized behavior, somatic problems, and the child's response to the examination did not make an additional contribution to the diagnosis.**

Conclusions.—**The findings support the need for a skilled psychological interview and a medical examination of a child alleged to have been sexually abused to make the diagnosis of sexual abuse. An interdisciplinary team appears to be a valuable approach for evaluating these children and their families.**

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The determination of whether a child has been sexually abused can be very difficult, and the consequences may be substantial. If child sexual abuse is not identified, there is a risk of continued abuse and serious sequelae. In contrast, if sexual abuse is erroneously diagnosed, the ramifications for the child, family, and alleged perpetrator might be very damaging. Pediatricians and other clinicians are therefore faced with a formidable challenge to make an accurate diagnosis when confronted with the possibility of sexual abuse.

The diagnosis of child sexual abuse is difficult for several reasons. There is often little or no clear history of abuse. Sexual abuse is usually committed secretly and incidents are rarely witnessed. Young children with limited verbal skills might be unable to describe their experience or their account might be questionable.[1] Even when it appears that children are describing abuse, doubts might persist about the veracity of their statements, particularly in the context of an acrimonious custody dispute.[2-4] As a result, there has been considerable controversy concerning the testimony of children as witnesses in legal proceedings.[5-8] Since many children may be unable or unwilling to discuss their abuse, anatomically detailed dolls have become a widely used adjunct to the clinical interview.[9,10] Through projective techniques children may disclose events they are unable to reveal verbally. Despite problems associated with children's disclosure, experts in the field of child maltreatment agree that the history obtained from the child is usually the most important evidence in diagnosing sexual abuse.[11]

Various behavior problems have been associated with child sexual abuse and may be useful diagnostically.[12-14] Inappropriately sexualized behavior appears to be strongly associated with a history of abuse.[12-14] However, it is often not clear what constitutes abnormal sexual behavior or knowledge.[1,15] For example, at what point is the frequency of masturbation excessive? It might also be unclear what stimulus led to the sexualized behavior; exposure to X-rated movies, observing intimate behavior between parents, or actual abuse could be responsible. In addition, highly sexualized behavior is sometimes seen in children who are not thought to have been abused.[15]

Sexually abused children have also been found to have increased psychological problems, including depression, anxiety and fears, aggression, and poor self-esteem.[12-14] However, none of these problems is unique to child sexual abuse. Even if psychosomatic disorders, such as enuresis, are more common in sexually abused children,[16] they are not specific to sexual abuse and are of limited utility in diagnosing sexual abuse. However, psychological problems and psychosomatic disorders should alert pediatricians to consider the possibility of abuse.

In addition to the history of abuse and psychological problems, the third area contributing to the diagnosis of child sexual abuse is the medical evidence. Normal examination results, however, do not rule out the possibility of sexual abuse. Indeed, many abused children have

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been found to have normal examination results.[17-19] Although some investigators have reported high rates of abnormal physical findings among sexually abused children,[20-22] methodological problems, such as a lack of comparison groups, render many of the findings difficult to interpret.

Considerable uncertainty remains in distinguishing abnormal from normal anatomy.[11,17,19] For example, several studies of the horizontal diameter of the vaginal opening in prepubertal girls have yielded discrepant results.[17-19,23-25] Other physical findings are thought to be clearly abnormal, but might not be specific to sexual abuse: erythema in the genital area is an obvious example.[17] Only a minority of sexually abused children have unequivocal physical evidence of abuse (eg, a gonorrheal vaginal discharge).

There is a consensus in the field of child maltreatment that the state of the art in assessing possible child sexual abuse is the interdisciplinary team evaluation.[11,26-28] This approach allows for the necessary integration of the social, psychological, and medical evidence in a comprehensive assessment, and avoids relying on any single aspect of the evaluation. The interdisciplinary team still rests on the expertise of its members, and the collective misinterpretation of information remains a risk. Nevertheless, the interdisciplinary evaluation is a theoretically sound approach to the diagnosis of sexual abuse, as well as to other forms of child maltreatment.

Despite the approval of an interdisciplinary approach, many children alleged to have been sexually abused do not appear to have received an interdisciplinary evaluation. Child protective services generally have limited access to mental health and pediatric providers with expertise in the area of sexual abuse. In addition, there frequently is a reliance on the medical examination, particularly by the law enforcement and judicial systems, while the value of other relevant information might be considered less seriously. It is noteworthy, however, that there have not been any studies, to our knowledge, of how information is integrated in the interdisciplinary process.

The primary goal of the present study was to examine how the history, psychological evaluation, medical examination, and child's response to the examination contributed to a diagnosis of child sexual abuse by an interdisciplinary team.

SUBJECTS AND METHODS

Sample

The sample consisted of 132 children who were referred to an interdisciplinary outpatient clinic for evaluation of possible sexual abuse. All children seen consecutively between September 1989 and June 1990 were eligible for the study. Only one parent refused to participate. The clinic is based in an urban teaching hospital serving a low-income, inner-city, and largely minority population. All children younger than age 12 years seen in the pediatric emergency department or one of the affiliated primary care clinics with a suspicion of sexual abuse are routinely referred to the clinic for evaluation. Thirty-one percent of referrals were made from the above sources, 52% from child protective services, 3% by the police, and 14% from other sources. The children were seen several weeks following an allegation of possible sexual abuse. The case histories varied markedly, ranging from rather vague suspicions to witnessed incidents of intercourse. The referrals were screened by a nurse and all cases met the criterion of possible sexual abuse.

The Clinic

The clinic was established at the University of Maryland Hospital, Baltimore, in 1983 and the team consists of a pediatrician, child psychologist, social worker, and nurse. Background information is obtained from the referring party. The assessment is conducted in one afternoon and consists of a social worker's interview of the parent(s) or guardian, a psychological assessment of the child, and a medical evaluation. The team considers all the available information and a decision is reached about the likelihood of sexual abuse. Any inappropriate sexual contact (excluding voluntary sexual activity between peers that appears to be within the normal range for the children's age) is considered abuse, regardless of the alleged perpetrator's age or relationship to the child. The conclusions from the evaluation are communicated to the family, along with specific recommendations for appropriate interventions.

Procedure

The interdisciplinary team evaluated all the children seen in the clinic, and the data were gathered prospectively. The social work assessment included a history of the alleged abuse, the family's response to the allegation, the involvement of public agencies, and sources of support to the family. In addition, the social worker assessed the functioning of the family, parental concerns regarding the child, and access to services. During the psychological assessment, the child's emotional and developmental status were evaluated, along with the child's account of the alleged abuse. Anatomically detailed dolls were used, depending on the clinical situation. The child's sense of safety and available support were also addressed.

Following obtainment of a medical history, a brief general examination was performed by a pediatrician. The genital examinations were done in the supine frog-leg position using a halogen lamp without magnification. The anal region was examined in the supine or prone knee-chest or lateral decubitus position. Physical characteristics of the genitalia were recorded on a precoded form, following the descriptions used by Emans et al[17]; neither a colposcope nor otoscope was used in the examination. The maximum transverse diameter of the hymenal opening was measured relative to the known width of the examiner's index finger. The pediatrician rated on five-point Likert scales the response of the child to both the general and genital examination, following efforts to allay anxiety concerning the examination.

Psychosomatic Problems and Sexualized Behavior

Problem behaviors were assessed using the Child Behavior Check list (CBCL),[29] completed by each child's parent or guardian ($N = 132$). The CBCL is a standardized screening instrument for assessing a child's behavior. It consists of 118 items that yield scores on different scales, including psychosomatic and sexual problems. A score greater than 70 is expected among approximately 2% of children in a random sample and corresponds to a problem in the clinical range.[29]

Abuse Severity Index

To examine how the severity of the abuse might influence the team assessment, the following three variables pertaining to the alleged abuse were combined in a scale: the nature of the abuse, the relationship of the perpetrator to the child, and the proximity of the perpetrator's residence to the child. Each of these variables was rated on a three-point scale, with the most harmful characteristics (ie, intercourse, abuse by a parent, and abuse by someone living in the home) scored as a 3; a total score of 9 represented the most severe abuse. These variables were selected based on previous research suggesting that more intrusive abuse (eg, intercourse compared with fondling), abuse by someone closely related to the child, and abuse by someone living in the child's home are particularly harmful to the child.[12,30,31] Other variables of interest, such as the frequency of the abuse or the use of force, were excluded because that information was often unavailable.

Table 1.—Characteristics of Alleged Perpetrators

Characteristic	No. (%) of Subjects (n = 89)
Sex	
Male	66 (74)
Female	4 (4)
Unknown	19 (21)
Age, y	
<12	9 (10)
12-19	24 (27)
20-60	33 (37)
>60	1 (1)
Unknown	22 (25)
Relationship to child	
Biological parent	9 (10)
Stepparent	5 (6)
Sibling	6 (7)
Other family member	14 (16)
Friend/neighbor	28 (31)
Sitter	7 (8)
Stranger	1 (1)
Unknown	19 (21)
Residence	
Same home	28 (31)
Elsewhere, visits	18 (20)
Other	21 (24)
Unknown	22 (25)

Table 2.—Characteristics of the Abuse

Characteristic	No. (%) of Subjects (n = 89)
Type of abuse*	
Genital-genital	20 (22)
Oral-genital	11 (12)
Digital-genital	16 (18)
Fondling	20 (22)
Other	3 (3)
Unknown	31 (35)
Frequency of abuse	
Once	28 (31)
Occasionally	14 (16)
Frequently	7 (8)
Unknown	40 (45)
Location of abuse	
Child's home	31 (35)
Perpetrator's home	20 (22)
Friend's home	4 (4)
Public	8 (9)
Unknown	26 (29)

*More than one type of abuse might have occurred.

RESULTS

The mean (SD) age of the 132 children was 6.0 (3.0) years; 83% were girls and 63% were black. At the time of the clinic evaluation, 74% were living with their mother, 11% were living with both parents, 11% were living with their extended family, 2% were living with their father, and 2% were in foster care.

Based on all the available information, the likelihood of abuse was rated by the team as "low" in 30% of the 132 children (no substantial psychosocial or physical findings), "possible" in 12% (suggestive psychosocial evidence without physical findings), "moderate" in 5% (suggestive psychosocial evidence and physical findings compatible with, but not necessarily indicative of, abuse), and "high" in 52% (clear disclosure by the child or physical findings indicative of abuse). In 2% of cases the team could not assess the likelihood of abuse.

The characteristics of the alleged perpetrators and of the abuse, excluding cases that were rated as having low likelihood of abuse or that were unrated, are presented in Tables 1 and 2, respectively. A perpetrator was identified in 78% of these cases. Most of the alleged perpetrators were male, nearly one third of them lived in the same house as the child, more than one third were family members, and more than one third were younger than age 20 years.

Most of the abuse involved genital contact, although almost a quarter of the children were fondled over their clothes. Some children were subjected to more than one form of abuse. In one third of cases, the abuse was alleged to have been a single incident, and to have occurred in the child's home. Quite often, the specific details of the alleged abuse were not available, even when it seemed likely that the child had been abused.

Fourteen percent of the children scored in the clinical range (ie, a score >70) on the CBCL for somatic complaints (N = 132), and 23% did so for sexual problems (n = 71). Since the CBCL only includes a sexual problems score for boys aged 4 to 5 years and girls aged 4 to 11 years, data were available on only 71 children (54%). Specific somatic complaints included aches and pains (10% of children), headaches (6%), and enuresis (14%), and one child (0.8%) was described as encopretic. Parents reported that 32% of the children masturbated "too much."

Complete information was available on 99 children. Thirty-two percent of the children gave a clear verbal disclosure of abuse, and an additional 27% provided a partial disclosure. A partial disclosure included suggestive doll play or an inconclusive account of alleged abuse. The pediatricians described 59% of the children as having normal examination results, 3% as having abnormal examination results *not* due to sexual abuse, 10% as having abnormal examination results compatible with sexual abuse (eg, a thickened hymenal edge without other signs of trauma), and 28% as having abnormal examination results indicative of sexual abuse (eg, hymenal scarring). For statistical comparisons, the children having normal examination results and those having abnormal examination results *not* due to sexual abuse were combined.

Of the 28 children who had abnormal examination results indicative of abuse, *all* were rated by the team as moderately or highly likely to have been sexually abused regardless of whether or not the child disclosed the abuse (Table 3). Of the nine children with abnormal examination results compatible with abuse, eight (89%) were rated as having moderate to high likelihood of abuse. Sixty-two children had normal physical examination findings; of these, 19 (31%) fully disclosed abuse and 18 (29%) were rated as having moderate to high likelihood of abuse. The credibility of one child's disclosure was strongly doubted. Thus, given either full disclosure or an examination finding indicative of abuse, the probability of a rating of moderate to high likelihood of abuse approached 100%. Alternatively, the team was unlikely to conclude a moderate or high likelihood of abuse without either physical evidence or disclosure (Fisher's Exact Test; $P = .01$). Only one (3%) of the 29 children with normal examination findings and no disclosure was rated as having moderate

Table 3.—Team Rating of Likelihood of Sexual Abuse by Disclosure and Medical Examination Results

Findings	Likelihood of Abuse No. (%) of Subjects: Low to Possible (n=36)	Likelihood of Abuse No. (%) of Subjects: Moderate to High (n=63)
Normal examination findings and		
No disclosure	28 (97)	1 (3)
Partial disclosure	6 (43)	8 (57)
Full disclosure	1 (5)	18 (95)
Examination findings compatible with abuse and		
No disclosure	1 (25)	3 (75)
Partial disclosure	0	5 (100)
Full disclosure	0	0
Examination findings indicative of abuse and		
No disclosure	0	7 (100)
Partial disclosure	0	8 (100)
Full disclosure	0	13 (100)

Table 4.—Physical Findings by Pediatrician's Overall Rating of the Physical Examination in Girls

Finding*	Physician Rating of Examination Findings, No. (%) of Subjects: Normal (n=50)	Physician Rating of Examination Findings, No. (%) of Subjects: Abnormal (n=32)	χ^2
Vaginal opening diameter >4 mm	24 (48)	25 (78)	7.4†
Acute trauma	0	0	NA‡
Scarring	0	17 (53)	34.7†
Adhesions	1 (2)	5 (16)	5.6§
Increased friability	1 (2)	1 (3)	0.1
Discharge	3 (6)	2 (6)	0.1
Hymen symmetrical	26 (52)	8 (25)	5.9§
Hymen discontinuity	0	10 (31)	17.8†
Hymen rounded	5 (10)	16 (50)	16.4†
Hymen bumps	8 (16)	11 (34)	3.7
Hymen clefts	7 (14)	8 (25)	1.6

*More than one finding might have been present.
†$P<.0005$.
‡NA indicates that a χ^2 could not be calculated because cell size was too small.
§$P<.05$.

to high likelihood of abuse, based on other information, such as highly inappropriate sexual behavior.

The physical findings that discriminated normal from abnormal genital examination findings for girls were analyzed using χ^2 (Table 4). Individual genital findings were first noted before making an overall assessment of the genital examination. Adhesions, hymenal scarring, asymmetry, discontinuity, and rounding were more prevalent in girls with abnormal findings. Girls with abnormal findings were more likely to have a vaginal opening with a horizontal diameter of greater than 4 mm. There was a significant moderate correlation of .40 between increased size of the opening and older age; the likelihood of abuse and age were also significantly correlated ($r=.19$; $P<.05$). However, it is important to note that, with the exception of scarring and hymenal discontinuity, all other physical findings were present in both groups of girls.

Medical data were available on 17 boys. Anal scarring was found in three boys (18%), fissures in two boys (12%), and gaping in one boy (6%) (>10 mm at the mucocutaneous junction). None of the boys had abnormalities of their genitalia or a penile discharge.

There were very similar responses by the children to both the general and genital examinations. Most of the 99 children were cooperative, 88% for the general examination and 85% for the genital examination. The child's response to the examination was not related to the pediatrician's assessment of the examination, the Abuse Severity Index, the team's rating of the likelihood of abuse, the child's behavior profile on the CBCL, or the child's disclosure of abuse. Only a history of genitourinary symptoms was correlated with greater resistance to the examination ($r=.33$; $P<.01$).

COMMENT

The major finding was that both the child's disclosure of abuse and the physical examination findings significantly contributed to the team's assessment of abuse; without either kind of evidence, the team was unlikely to conclude that the child had been abused. Less direct evidence, such as the child's behavior, was unlikely to lead to an assessment of probable abuse. However, a disclosure and physical findings were often *not* both present. In this study only 21% of the children assessed as moderately or highly likely to have been abused had fully disclosed such abuse *and* had examination results indicative of abuse. Forty-four percent of the children assessed as moderately or highly likely to have been abused had normal examination results, but had disclosed abuse. This finding supports the importance of the child interview in diagnosing the likelihood of sexual abuse.[11] The importance of the disclosure makes it necessary that evaluations of suspected sexual abuse be done by clinicians trained in eliciting sensitive information from children. The value of the child's disclosure in the evaluation of alleged abuse underscores the need for professionals involved in this field to recognize the importance of the child's account, regardless of the medical evidence.

A sizable proportion of sexually abused children, however, do not disclose their abuse, even to skilled interviewers. Furthermore, the disclosure might be unclear and not allow a firm conclusion as to the likelihood of abuse; in some instances the truthfulness might be in question. This study demonstrates the added usefulness of a medical examination for determining whether a child has been abused. Of the 63 children assessed as moderately or highly likely to have been abused, 44% had examination findings indicative of abuse. Since 25% of these children with abnormal examination findings indicative of abuse did not disclose at all and 28% partially disclosed, without the examination many of these children might not have been diagnosed as abused.

Abnormal medical examination results were almost always associated with an assessment of moderate or high likelihood of abuse. Many children reported to child protective services for sexual abuse are *not* examined physically. The present study strongly supports the need for a medical examination of all children suspected of being sexually abused. Both the child's disclosure and the examination findings contributed significantly to the team's diagnosis. However, in the presence of a clear and credible disclosure, the physical examination added little in terms of assessing the likelihood of abuse. Similarly, disclosure added little when there were examination findings indicative of abuse.

Nevertheless, it is appropriate for clinical reasons that both the child interview and examination be conducted. Aside from forensic concerns, medical and mental health problems need to be identified, and reassuring the child and parent when the examination finding is normal can be very helpful. Furthermore, a comprehensive psychosocial assessment of the child and family is needed to guide an appropriate treatment plan.

It is noteworthy that the severity of the alleged abuse, the child's age, the child's response to the examination, and the child's behavior profile, including the presence of somatic problems (eg, enuresis) and sexualized behavior, did not add significantly to the team's assessment of the likelihood of abuse. Although these factors did not contribute beyond the disclosure and/or the physical examination in shaping the team's assessment, the presence of somatic and sexual problems is important for planning treatment and may have alerted the family to the possibility of abuse.

The characteristics of the perpetrators are similar to those described in other studies, particularly when pertaining to young children.[20,22,32] For example, Kendall-Tackett and Simon[32] found that 97% of perpetrators were male, and only 1% were strangers. The relative youth of the perpetrators in the present study supports the notion that a substantial number of males who molest children begin to do so at an early age.[33] Most sexually abused children are victimized by familiar males who either live in or visit the home.

Characteristics of the abuse are also similar to findings in other studies. Prepubertal children have been found to be less likely to be penetrated vaginally compared with adolescent victims.[20] Emans et al[17] reported that 5% of the girls in their study had been vaginally penetrated. The number of abusive incidents reported varies greatly in different studies and it is likely that this information is quite unreliable, particularly when young children are involved.[17,20] Possibly, the guilt and pressures that can lead abused children to retract their disclosure might also induce them to report fewer abusive incidents. In addition, young children (eg, 4-year-olds) do not have a good understanding of concepts of time and number.

The abused children in the present study had significantly higher rates of somatic complaints and sexualized behavior compared with the normative population[29] and a local comparison group of nonabused children, matched on age and gender.[34] Other research on sexually abused children has also found an increased prevalence of somatic and sexualized behavior as well as an array of psychological problems.[12,13,16,35] Lusk and Waterman[13] suggest that the sexualized behavior may be due to a lack of inhibition of sexual impulses or a way of dealing with the abuse. The somatic complaints may be rooted in the anxiety and fear that many sexually abused children experience.[12-14] It is important to note that with the probable exception of sexualized behavior, the somatic symptoms and other behavior problems are not specific to sexual abuse.

The physical findings in this study are supportive of other research in which definitive medical evidence of abuse is lacking in many cases.[17,18] Forty-three percent of the 63 children assessed as moderately or highly likely to have been abused had normal examination findings. There is a need to consider the complete genital examination rather than rely on individual findings, such as the diameter of the vaginal opening. Of the 32 girls with abnormal examination findings, 78% had a vaginal opening larger than 4 mm, and of the 50 girls with normal examination findings, 48% had a vaginal opening larger than 4 mm; 4 to 5 mm has been reported as a "normal" maximum diameter in prepubertal girls.[18,23]

Most of the children cooperated for the examination, both for the general and genital aspects. Children who have been sexually traumatized might be expected to be anxious and resistant to the genital examination; alternatively, as a result of their sexual experiences abused children might be less inhibited and resistant. We found that their response to the examination was not related to the likelihood and severity of abuse, the presence of physical findings, or their behavior profiles; only a history of genitourinary symptoms was associated with greater resistance. Possibly, children who had been symptomatic were more likely to have had genital pain and to have been examined and had cultures taken, and were therefore more resistant. Since other developmental and personality characteristics can contribute to children's responses to physical examinations, the child's response to the examination is *not* a helpful indicator of sexual abuse.

There are a few limitations to the present study. The generalizability of the findings to other sexually abused children is uncertain given the clinic's referral process. For example, it is possible that relatively ambiguous cases were more likely to be referred to the clinic by protective services. However, the clinic procedure and population are similar to many other such clinics in the United States. Since the children were not examined immediately in our clinic, we were unlikely to detect acute findings. However, information on prior evaluations was generally presented to us. In addition, there is often a delay before children disclose their abuse. Therefore, it is possible that the study findings would have been similar had the evaluations been conducted within a few days of the disclosure.

Another limitation is the use of the team's assessment as the determination of whether the child was abused. Even though the team members had considerable experience working in the area of sexual abuse, it is possible that errors in judgment were made. We cannot assume that the interdisciplinary team diagnosis of abuse is always accurate. Many cases of suspected sexual abuse are ambiguous, and a conclusive diagnosis is not always possible. However, a skilled interdisciplinary assessment is probably the optimal approach to diagnosing sexual abuse.

IMPLICATIONS

A disclosure of sexual abuse by a child and abnormal genital examination results are important determinants of the diagnosis of sexual abuse. It is therefore important that all children who are alleged to have been sexually abused be interviewed *and* examined medically by professionals trained and skilled in this area. An interdisciplinary team assessment is a useful approach for integrating the social, psychological, and medical information needed to make accurate diagnoses of child sexual abuse.

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Steven H. Woolf, MD, MPH (*Arch Intern Med.* 1992;152:946-952)

Evaluation of Sexually Abused and Nonabused Young Girls for Intravaginal Human Papillomavirus Infection

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William W. Johnston, MD; William C. Phelps, PhD

• *Objective.*—The objective of this study was to compare the prevalence of intravaginal human papillomavirus-associated disease in two groups of girls to develop information regarding the means of transmission of anal-genital human papillomavirus disease.

***Design.*—A pair of parallel studies of prevalences of human papillomavirus infections in two populations of prospectively enrolled girls.**

***Patients.*—Index patients consisted of 15 consecutive girls aged 11 years or younger who were confirmed to have been sexually abused, had signs or symptoms of vaginal disease, and required generalized anesthesia for evaluation. Selection of nonabused control patients was based on negative findings from screening evaluations and physical examinations.**

***Main Outcome Measures.*—Prevalences of cervical-vaginal human papillomavirus infections in the two populations were compared. Vaginal wash samples from index and control patients were assayed for human papillomavirus 1, 2, 4, 6, 11, and 16 by reverse-blot and Southern transfer hybridization methods. Papanicolaou smears were examined from index patients.**

***Results.*—Vaginal wash samples from five (33%) of 15 index patients were positive for human papillomavirus 6, 11, or 16, compared with none of 17 controls. The presence or absence of external anal-genital warts was not correlated with results from the assay of intravaginal samples. Blinded readings of vaginal exfoliative cytologic findings of the index patients showed koilocytosis, atypia, or inflammatory reactions in four of five human papillomavirus-positive girls, and normal cytologic findings in one human papillomavirus-positive girl.**

***Conclusion.*—These findings support other studies that indicate that sexual contact is a major route in the transmission of anal-genital human papillomavirus-related disease in children. Evaluation of intravaginal specimens was required to identify human papillomavirus-infected girls since the results of the wash samples were not correlated with the presence or absence of external anal-genital warts.**

(*AJDC.* 1992;146:694-699)

A substantial body of epidemiologic data indicates that human papillomavirus (HPV)–related diseases of the adult genital tract are transmitted primarily through sexual contact.[1] In contrast, there have been conflicting reports about the means of transmission of anal-genital warts to postneonatal children. The major area of uncertainty is whether the primary mode of transmission of genital warts to children is similar to that in adults; ie, sexual contact. This question has been studied primarily through the assessment of children who have been identified as having genital warts and were evaluated for possible sexual abuse. However, the methods of evaluating for sexual abuse have varied greatly, and, thus, reported rates of confirmed child sexual abuse in children with anal-genital warts have ranged from 0% to 91%.[2,3] Evaluation of abused girls for intravaginal HPV-related infection has not been recommended, and no data on the prevalence of intravaginal HPV infection in children have been published.

The intravaginal microbiologic findings of nonabused young girls have not been well characterized because of the social and technical limitations in acquiring samples. Prevalence studies in defined populations represent a means of investigating the relationship between sexual abuse and anal-genital HPV infection in children. However, because of the limitations on sample collection, studies to identify intravaginal HPV infection in either sexually abused girls or nonabused girls have not been reported.

The present study documents the prevalence of a selected number of HPV types from vaginal wash samples of two groups of young girls whose status regarding sexual abuse was fully characterized. The first group comprised girls who had been victims of invasive child sexual abuse, while girls in the second group had not been sexually abused. This study differs in two respects from others that have examined the means of transmission of anal-genital HPV disease in children. In this study, two

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populations of girls were compared, and the study focused on the diagnosis of intravaginal HPV disease as manifested by HPV, DNA, and cytologic findings, rather than on external genital warts.

SUBJECTS AND METHODS

Selection of Index Patients

The Duke Child Protection Team examines approximately 250 girls per year for suspected child sexual abuse, and abuse is confirmed in about 40% of examined girls. The index population comprised 15 girls aged 11 years or younger who were Tanner stage 1 or 2 in sexual development and who had been referred to the Duke Child Protection Team for evaluation of suspected child sexual abuse. The index population included all girls from a 4½-year period beginning in 1986 who fulfilled the following criteria: (1) The Child Protection Team completed the evaluation for suspected child sexual abuse. (2) The girls had a history of symptomatic vaginal disease (ie, discharge, bleeding, or pain) that required a medical examination. (3) Generalized anesthesia was used because the girls were unable to tolerate the examination while awake. (4) The girls were confirmed to have been abused by the Child Protection Team. Examinations using anesthesia were indicated when there were persistent medical signs or symptoms and the child could not tolerate the examination while awake. Index patients were referred for an examination with anesthesia for evaluation of acute injury and/or recurrent or chronic symptomatic vaginal disease manifested as bleeding, discharge, pain, or lesions (Table 1).

Table 1.—Genital Signs and Symptoms of Index Patients (n=15)

	No. of Patients
Presenting complaints	
Vaginal discharge	
Chronic or recurrent	7
Acute	2
Vaginal bleeding	5
Labial abrasions	3
Perivaginal lesions	
Perivaginal condyloma acuminatum	3
Perivaginal molluscum contagiosum	1
Perianal lesions	1
Additional findings during anesthesia administration	
Scars, tears, notches, or distortions of hymen	8
Hymenal opening transverse diameter ≥8 mm	10
Changing external examination results with serial evaluations	2
Abnormal external genital examination results	15

Selection of Control Patients

Control patients were recruited from the pediatric clinics at the Duke Eye Center, Durham, NC. They were girls aged 11 years or younger and Tanner stage 1 in sexual development who had been scheduled to receive ophthalmic examinations or procedures while receiving generalized anesthesia. Control patients underwent a screening assessment for sexual abuse because child sexual abuse is a common problem and nonabuse of this population could not be assumed.[4-6]

The median age of the index population was 59 months, with a range of 23 to 131 months. The median age of the control population was 34 months, with a range of 3 to 68 months (Table 2). The control population was significantly younger than the index population ($P=.006$; two-sample Wilcoxon's rank sum test). Eight (53%) of the index children were black and seven (47%) were white. Of 17 controls, six (35%) were black and 11 (65%) were white. The groups did not differ significantly in the percentage of black children ($P=.47$; Fisher's Exact Test).

Evaluation for Child Sexual Abuse

Methods used in evaluating the index patients for sexual abuse have been described[7] and follow currently recommended procedures, including parent interviews and child interviews and examinations.[8] Five groups of data were obtained: (1) a review of the behavioral history of the child, (2) a review of the medical history of the child, (3) multiple diagnostic interviews with the child, (4) a forensic medical examination, and (5) assessment for other sexually transmitted diseases. In the present study, "disclosure" refers to the detailed verbalization by the child or other witness of a specific sexually abusive act. Perpetrators were "identified" if the child or a caretaker had provided specific description of the person as an assailant.

Child sexual abuse was confirmed on the basis of any of the following: (1) the child or a witness disclosed the abuse; (2) genital gonorrhea or acquired syphilis was diagnosed; (3) the genital examination results were abnormal, with findings clearly indicative of abuse as outlined at the 1985 National Child Sexual Abuse Summit meeting and subsequently updated[9-12]; (4) serial genital examinations showed changing abnormalities that were indicative of active sexual abuse; or (5) there was acknowledgment by the perpetrator.

The following methods were used in evaluating control patients for concerns of sexual abuse. At an eye center clinic visit, the study and procedure were described to the parents and child by a member of the Child Protection Team and informed consent was obtained. An intake questionnaire was administered by one of us (K.S.C.) that included questions about each of the following medical areas: chronic illness and previous medical interventions (five questions asked); medications (two questions); genitourinary signs and symptoms (nine questions); gastrointestinal signs and symptoms (three questions); vaginal signs and symptoms (five questions); and behavioral disturbances (10 questions). Open questions were asked regarding any concerns the parents may have had concerning physical or sexual abuse. The physical examination of the external genitalia was performed at the time of administering anesthesia. The evaluation did not include a separate diagnostic interview with the child.

Table 2.—Study Populations

Characteristic	Index Patients (n=15)	Controls (n=17)	*P*
Median (range) age, mo	59 (23-131)	34 (3-68)	.006 (Wilcoxon's rank sum test)
Race, No. (%) of patients			
Black	8 (53)	6 (35)	.47 (Fisher's Exact Test)
White	7 (47)	11 (65)	
Assays positive for HPV6, 11, or 16, No. (%) of patients	5 (33)*	0	.015 (Fisher's Exact Test)

*HPV indicates human papillomavirus infection. The HPV types identified included HPV6 in two patients and HPV11, HPV 6/11, and HPV16 in one patient each.

The study protocol required that parents be informed of findings that raised concerns about possible child sexual abuse and the parents were aware that a report of suspected sexual abuse would be made should findings strongly indicate abuse. The study was approved by the Duke Institutional Review Board and written parental consent was obtained.

Physical Examination and Collection of Specimens

The external genital examination for both groups of children included inspection of the labia and introital area for redness, discharge, lesions, or injuries; identification of hymenal type and contour; and measurement of the horizontal diameter of the hymenal opening.[13] Samples obtained included vaginal swabs and washes. Intravaginal samples from index patients were obtained during direct visualization of the vagina and cervix, and cervical-vaginal Papanicolaou smears were obtained. Vaginal wash material was collected through a flexible, small-bore plastic catheter that was fitted to the end of a 10-mL syringe. The catheter was inserted through the hymenal opening, and 10 mL of Dulbecco's phosphate-buffered saline was washed in and out of the vagina two or three times. Direct intravaginal visualization was not attempted in the control children and therefore Papanicolaou smears were not obtained.

Virologic Diagnosis

Plasmid-cloned isolates of HPV1, 2, and 4 have been previously described.[14] The HPV6 probe consists of the Fnu4H1 (b. 509) fragment to the MstII (b. 4520).[15] The HPV16 consists of the full genome from a pUC18 clone derived from the prototype.[16] The HPV11/pUC18 was cloned from a patient specimen (L.T.G, unpublished data, 1991).

The HPV DNA fragments were isolated electrophoretically and labeled with ^{32}P using random oligonucleotide primers for use as probes.

HPV DNA Analysis

Cellular DNA was isolated from the pellet of vaginal wash material by overnight digestion, phenol extraction, and alcohol precipitation. The extracted DNA was digested with RNAse, extracted with phenol, and alcohol precipitated a second time. The concentration of DNA was determined with a spectrophotometer. The range of DNA extracted from samples from index patients was 630 ng to 2.25 μg and that from control patients was 315 to 630 ng. A minimum of 300 ng was required to complete the study protocol.

Reverse Southern Hybridization

Reverse Southern hybridization for HPV1, 2, 4, 6, 11, and 16 has been previously described.[17,18] Briefly, 200 ng of each of HPV types 1, 2, 4, 6, 11, and 16 was immobilized on a nylon filter. The probe consisted of 50 to 100 ng of patient DNA that was labeled with ^{32}P using random nucleotide primers. Hybridization was performed at 65°C. The sensitivity of this assay was less than or equal to 1 pg of HPV DNA in 1 μg of cellular DNA.

Table 3.—Type of Sexual Abuse Disclosed (n=15)*

Site of Contact†		No. of Index Children
Assailant	Child	
Penis	Vagina	9
Penis	Anus	4
Penis	Mouth	2
Finger	Vagina	2
Mouth	Vagina	1

*Five children disclosed multiple types of abuse.
†The site of contact was unknown for two children.

Southern Transfer Hybridization

Two hundred nanograms of cellular DNA from each index and control patient was digested with the restriction endonuclease enzymes, *BamHI* or *Pst I*, and analyzed with Southern transfer hybridization procedures.[19] Samples were separated by electrophoresis, transferred to nylon filter, and probed with ^{32}P-labeled HPV6/11 and HPV16. Hybridization produced a readily visible signal with less than 0.2 pg of HPV DNA per 200 ng of cellular DNA.

Cervical-Vaginal Cytologic Findings

Cervical-vaginal swabs were collected from index patients for cytologic examination. The preparations were interpreted by a single observer (W.W.J.), who was blinded to the results of the HPV assays. Descriptive observations were made and findings were categorized according to the Bethesda System.[20] Koilocytes are mature squamous cells characterized by a large perinuclear cavity with sharp borders. The cellular cytoplasm is dense and the nucleus shows varying degrees of degeneration. These cells are commonly present in HPV-infected lesions.

RESULTS

Control and Index Patients

Fifteen index patients met the criteria for entry into the study. Thirteen girls (87%) gave a full disclosure of sexual abuse and two (13%) gave a partial disclosure of sexual abuse. Thirteen girls had abnormal examination findings of the introital area or hymen that were consistent with healing or healed trauma from sexual abuse (Table 1). The 15 index patients came from 15 separate households and no index patient was related to any other patient.

Seventeen control patients underwent a behavioral, medical, and physical screening evaluation for child sexual abuse and had negative findings. A vaginal wash sample was obtained from each of these girls for evaluation for HPV. Two potential control patients were omitted from the study because of concerns of possible abuse that were identified during the screening evaluation. Both children disclosed their abuse and identified the perpetrators.

Perpetrators

Five (33%) of the index children had been assaulted by single perpetrators, four (27%) had been assaulted by multiple perpetrators, three (20%) disclosed abuse but did not identify a specific perpetrator(s), and three (20%) identified one perpetrator with at least one additional perpetrator suspected. All identified perpetrators were either related to the child or had access to the child because of a relationship with another member of the family.

The types of abuse that were disclosed by the index patients are listed in Table 3. Eleven children (73%) described penetrating penile-vaginal or penile-anal abuse, and two (13%) described digital abuse. Two children (13%) were unable to give details of their assault.

HPV DNA Assay

Vaginal wash samples from five (33%) of the 15 index patients were positive for HPV using Southern transfer hybridization. Four (80%) of these five were HPV types 6 or 11, and one was HPV type 16 (Table 2). The results of the reverse-blot assays corroborated the findings of the Southern transfer hybridization assays (Figs 1 and 2). Labeled DNA from index patients did not hybridize with HPV1, 2, or 4 on reverse blots. The prevalences of HPV

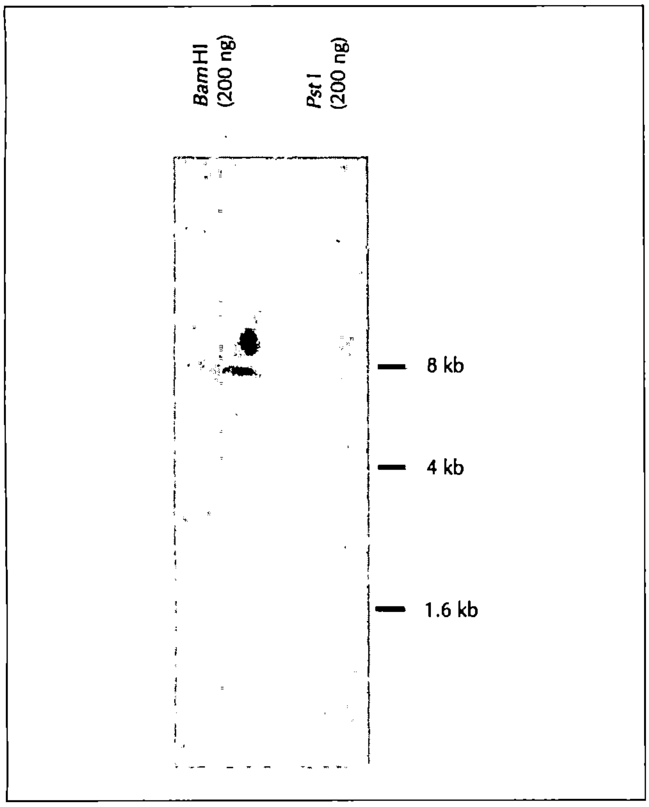

Fig 1.—*Restriction endonuclease digestion results from a cervical-vaginal wash specimen.* Bam*HI and* Pst *I demonstrated fragments characteristic of HPV6a.*

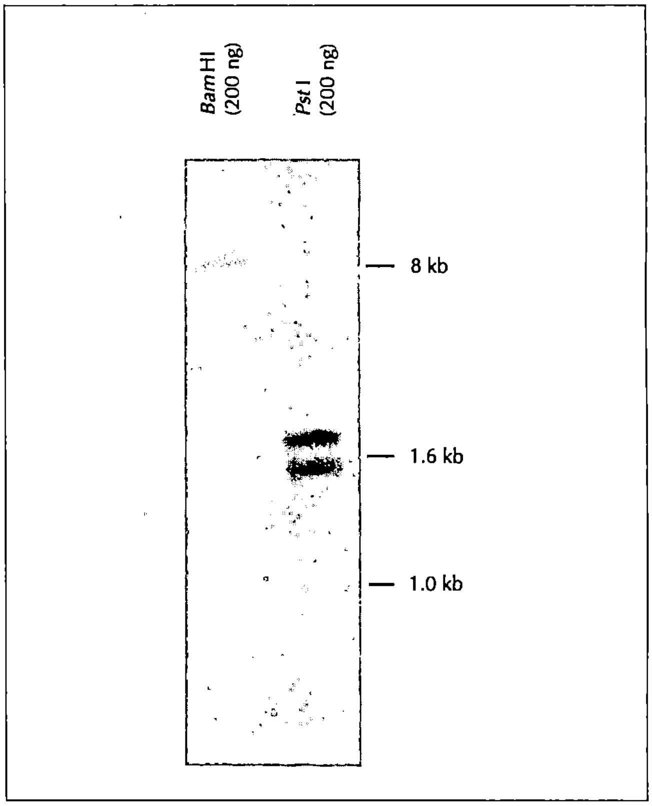

Fig 2.—*Restriction endonuclease digestion results from a cervical-vaginal wash specimen.* Bam*HI and* Pst *I demonstrated fragments characteristic of HPV11.*

Table 4.—Relationship Between Presence or Absence of External Genital Lesions and Positive or Negative Assay Results From Intravaginal Wash Samples For Index Patients With Human Papillomavirus (HPV) Infection

Clinical Evaluations	Vaginal Wash Assay Results, No. of Patients: HPV DNA Positive	Vaginal Wash Assay Results, No. of Patients: HPV DNA Negative	Total
External anogenital warts present			
Perianal	0	1	1
Perivaginal	2	1	3
External anogenital warts absent	3	8	11
Total No. of index patients	5	10	15

DNA from the two study populations, 0 of 17 controls vs five of 15 index cases, differed significantly ($P = .015$) using Fisher's Exact Test. The 95% confidence interval for HPV positivity in the index population was 9% to 57%.

External Genital Warts

The relationship between the presence or absence of external genital lesions and intravaginal infection is shown in Table 4. Four of the index patients had clinically evident external anal-genital warts, one in the perianal area and three in the perivaginal area. Two girls also had an intravaginal specimen that was HPV positive and two did not. Three (60%) of the five girls who had HPV-positive intravaginal specimens did not have identifiable external genital warts. Biopsy material of external lesions from one patient was examined for HPV DNA, and both wash and biopsy results showed HPV6a.

Cytologic Findings

Of the five girls with HPV-positive wash specimens, only one had cytologic findings that included koilocytosis (Fig 3). Cytologic findings from a second HPV-positive child showed a severe acute inflammatory reaction in which the parabasal cells were surrounded by a dense aggregation of polymorphonuclear leukocytes. The nuclei of parabasal cells showed atypia with darkening of the nuclear chromatin, thickening of the nuclear envelope, and increased nuclear to cytoplasmic ratio. For the third child, cytologic findings were restricted to chronic inflammatory reactions showing lymphocytic and monocytic cellular predominance and relatively fewer parabasal cells. Cytologic findings for the fourth child included a severe acute inflammatory reaction with a predominance of polymorphonuclear leukocytes and parabasal cells that showed mild perinuclear clearing but not overt koilocytosis. The fifth child had normal cytologic findings, without evidence of inflammatory reaction, atypia, or koilocytosis.

Cytologic examinations from the 10 index girls who had negative HPV DNA vaginal washes showed neither cellular reactions suggestive of HPV infection nor acute or chronic inflammatory reactions.

COMMENT

The index patients represent a subpopulation of sexually abused girls who were particularly symptomatic from the trauma that they had experienced and whose abuse

Fig 3.—*Papanicolaou smear from human papillomavirus-positive child, demonstrating koilocytic findings in squamous cell. The nucleus is marginated and condensed, the cell is enlarged, and a halo surrounds the nucleus (original magnification ×320).*

was probably unusually severe. At least four (27%) of the 15 patients had been abused by multiple perpetrators. All had signs or symptoms of intravaginal disease. Most of the types of disclosed abuse that they experienced were invasive. The 33% rate of recovery of HPV DNA from patient samples is similar to the recovery rate of HPV from a sexually at-risk adult population that was studied using a dot-blot hybridization method.[21]

Using the Southern transfer hybridization method, the recovery rate of HPV DNA from index cases was slightly higher than the 15% rate of recovery from another at-risk adult population.[22] Results from the HPV assays of the index children therefore closely resemble results from adults who are highly sexually active. Even so, the 33% prevalence rate of HPV from the index population is expected to be an underrepresentation of the true prevalence of this infection in children who have been severely abused because sample sizes were small, assays for only six HPV types were performed, and only a single sample was taken from each child.

In adults, the primary means of transmission of HPV-related genital disease is through sexual contact. Evidence of sexual transmission in adults comes from studies of couples; 90% of new sexual contacts of persons with genital warts result in the development of genital lesions.[23] In other studies, more than 60% of adults in established relationships with partners who have genital warts were concordant for the presence of lesions.[24,25] Similar data for child victims of sexual abuse are not available because, in these cases, perpetrators identified by children are rarely charged with the offense. This effectively prohibits any evaluation for sexually transmitted diseases.

Other evidence that HPV infection is sexually transmitted in adults includes data showing a relationship between prevalence of HPV infection and numbers of sexual partners. In adults, these two factors increase proportionally.[26,27] Similarly for children, a recent study has shown a significant association between the presence of multiple, other sexually associated organisms in children who have genital warts and who have been abused by multiple perpetrators.[3]

Medical literature on children with anal-genital papillomavirus disease contains conflicting information about sexual contact as the means of transmission of this infection to children. Unfortunately, many of these reports and studies were done prior to the development of currently established methods for evaluating child sexual abuse. Most of these earlier reports did not use a sexual abuse evaluation process, which must include a diagnostic interview of the child and parent by a skilled interviewer and a forensic genital examination by a qualified examiner. Rather, most of the earlier reports relied on the child to volunteer the disclosure and categorized nondisclosing children who had not received a thorough evaluation as nonabused.

Several of the more recent studies have also omitted any description of the evaluation methods and findings that they used to diagnose sexual abuse, or they have categorized children as nonabused when the child's status was inadequately documented or unknown.[2,28,29] Consequently, reported associations of sexual abuse with HPV transmission to children are likely to be inaccurately low. Despite the limitations in their diagnosis of sexual abuse, however, these earlier reports document that at least 50% of children with genital warts disclosed that they had been sexually abused.[30,31] The only published study using current diagnostic methods for child sexual abuse in girls having genital warts showed that 10 (91%) of 11 had been sexually abused. In that study disclosure of abuse was provided in 71% of cases, and in a similar study a high disclosure rate was also recorded.[3,32] Sexual abuse was confirmed in four of the five children aged 3 years or younger.[3] This strongly suggests that even in children who are preverbal or only marginally verbal the presence of genital tract lesions due to HPV is frequently associated with a confirmed diagnosis of sexual abuse.

The current study used the Southern transfer hybridization assay for several reasons. First, previous studies using this method have demonstrated that most genital papillomas of children are caused by HPV6 or 11 and only infrequently by HPV2, 16, or 18.[33,34] Other types are rarely or never identified in genital lesions of children. Consequently, our assay was designed to examine specimens for a limited number of HPV types. Second, because nonamplified DNA was measured, quantitative information was provided, and identification of the type was precise. Third, the method is the criterion standard.

In the present study, racial distribution of the index and control children did not differ significantly. The mean age of the control population, however, was significantly younger than that of the index population. The control patients were therefore closer in time to possible neonatal transmission of HPV, and they were also more likely to have difficulty in evaluations for sexual abuse due to their preverbal or poorly verbal developmental stages. These factors resulted in a conservative bias for the study.

Of particular concern for the HPV-positive children is that the long-term consequences of early exposure to this infection are unknown. Of note are reports from several medical centers about the increased incidence of genital-tract papillomavirus infections in female adolescents. Benign, dysplastic, and malignant HPV-associated lesions are also now being reported in this age range.[35-39] Because the length of time between HPV infection and progression to dysplastic and malignant stages may be quite long, some of these female adolescents may have acquired their infection prior to the legal age of consent for intercourse and through abusive sexual contact as a child.

The present data indicated that our index population of abused girls resembles populations of sexually active adults in the prevalence of intravaginal HPV DNA, in the presence of anal-genital lesions, and in cytologic findings. These children have acquired their internal genital HPV disease at very immature ages. Data regarding their prognosis and appropriate treatment are needed. Study findings also support other data that children presenting with anal-genital papillomavirus disease are at significant risk of having been abused and should be evaluated for possible sexual abuse and other sexually transmitted infections.

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Sexual Abuse of Children

The Detection of Semen on Skin

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• *Objective.*—The detection of semen on the skin of children who present within 72 hours of an episode of sexual assault is critical to medical, forensic, and legal personnel. The Wood's Lamp, a UV light that causes semen to fluoresce, and four forensic laboratory techniques were compared to determine their sensitivity and decline in sensitivity over time.

***Design.*—A descriptive study.**

***Participants.*—Eleven adult female volunteers.**

***Measurements/Main Results.*—Semen was placed on the skin of the volunteers. Samples of the dried semen were assessed during a 28-hour period with the Wood's Lamp, microscopy, the acid phosphatase assay, and two assays for the prostatic protein p30 (counterimmunoelectrophoresis and enzyme-linked immunosorbent assay). The intensity of the Wood's Lamp fluorescence of semen diminished dramatically by 28 hours; in contrast, the fluorescence of urine persisted up to 80 hours. Over time, the p30–enzyme-linked immunosorbent assay technique was more sensitive than microscopy, the acid phosphatase assay, and p30-counterimmunoelectrophoresis in detecting semen on skin.**

***Conclusions.*—The Wood's Lamp is not a sensitive screening tool and should be used with caution. To improve the detection of sexual abuse in children, we recommend that the p30–enzyme-linked immunosorbent assay be used because of its potential as a more sensitive assay than those in current clinical use.**

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National incidence studies reveal that approximately 1% of all children will experience some form of sexual abuse in a given year.[1] It is estimated that 45% of child sexual assault cases involve acts of molestation with genital contact without penile penetration.[1] Ejaculation may occur in these cases, making the presence of semen on a child's skin diagnostically important. Unfortunately, sensitivities of the routine screening and diagnostic tests for detecting semen on skin are unknown. These tests are used in acute cases of sexual abuse, cases seen within 72 hours of an alleged assault, and are not considered to be of value after that time.

Because children often present to a medical examiner days after an episode of sexual abuse, it is important to know how increasing time affects the results of these tests.[2] It is critical that clinicians and forensic scientists, understand the limitations of the diagnostic and screening tests used during the examination of the sexually abused child. This study was conducted to evaluate the sensitivity and specificity of the Wood's Lamp (WL) and the sensitivities of four diagnostic techniques used to identify semen on a victim's skin.

The WL, a screening tool used within 72 hours of an assault, creates a UV illumination that detects semen fluorescence.[3] Detection of semen fluorescence is especially helpful in cases in which a young child's ability to give a history of sexual assault may be limited. Wood's Lamp fluorescence is not specific to semen since many other substances that may be found on skin have fluorescent properties. Despite its widespread availability and simplicity, the WL technique is not standardized, and there have been no studies to date regarding its specificity or sensitivity over time. Typically, when a fluorescent area is visualized during the examination of an abused child, a swab or scraping of the area is obtained.[4] The swab is further analyzed for semen by forensic analyses.

Three forensic techniques commonly used in the analyses of semen evidence were concurrently examined in this study: (1) sperm detection by microscopy, (2) the assay for acid phosphatase (ACP), and (3) the detection of the prostate-specific protein, p30 by counterimmunoelectrophoresis (CIE). A fourth technique, the detection of p30 by an enzyme-linked immunosorbent assay (ELISA), was also examined. These tests vary in their sensitivity and specificity. Detection of spermatozoa by microscopy is considered diagnostically specific for sexual contact.[5] Acid phosphatase is less specific since it is present in the vaginal fluid and urine of women, albeit at much lower levels than in semen.[6,7] It is not known if ACP is present in the vaginal fluid or urine of prepubescent girls; it is present at very low levels in the urine of prepubescent boys.[8] Negative ACP test results have no diagnostic value since they do not necessarily indicate the absence of semen.[9] Prostate-specific protein, p30 (also called prostate-specific antigen), is found in seminal fluid and urine of men, and under normal circumstances is absent from all other body fluids in males and from all tissues and body fluids in females.[10,11] The p30-ELISA test is approximately 100 times more sensitive than the ACP or p30-CIE tests. Although these semen markers have been studied in

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postcoital vaginal samples and their specificity has been outlined, little is known about the decay in their sensitivities over time when samples are obtained from skin.

The following questions were addressed by this study: (1) How does the pattern, color, and intensity of WL fluorescence of semen change over time? (2) Do nonsemen substances, likely to be present on the skin of children referred for sexual abuse examinations, cause false-positive WL readings (thereby compromising specificity)? (3) How does the sensitivity of microscopy, ACP, and p30 techniques, analyzed from semen samples taken from the areas of WL fluorescence, change over time? (4) Can forensic tests detect semen in areas that are WL negative? Although adult subjects participated in this study, our intent was to address these questions as they specifically relate to the examination of child sexual assault victims.

SUBJECTS AND METHODS

Preliminary Testing

Preliminary testing was conducted to provide general estimates of the effects of time and body location on the WL fluorescence of semen. Since observations of semen on skin during an 80-hour period demonstrated that semen fluorescence became faint after the first 28 hours, this period was chosen for the study. There was no remarkable difference in semen fluorescence and semen analysis when semen placed on the inner thigh was compared with semen placed on the ventral forearm; therefore, the forearm was chosen for the site of study.

Preliminary testing was also conducted to identify substances that might be present in child sexual assault cases and have the potential of causing false-positive WL readings. These included infant formula, milk, cola, moisturizing lotions, petroleum jelly, a common lubricating jelly (K-Y Jelly, Johnson & Johnson, Skillman, NJ), a contraceptive foam and cream, and urine. The fluorescence of most of these substances differed from semen fluorescence in color, texture, or pattern. Urine and formula exhibited a color and pattern of fluorescence similar to semen. Moreover, urine fluorescence persisted through the preliminary observation period of 80 hours. Because urine has the potential of being present in the perineal area of young children and the fluorescence of urine could be confused with that of semen, urine was included in the study to examine its potential for generating false-positive WL readings.

Subjects and Sample Collection

Eleven women were recruited from two universities in northern California during February and March 1990, and informed consent for participation in the study was obtained. Each subject obtained a semen sample from a male partner on the evening prior to or on the morning of the study. Samples collected in the evening were promptly refrigerated after collection. (During preliminary testing, the fluorescent and forensic properties of refrigerated semen were found to be no different than those of fresh semen.) On the morning of their study participation, subjects were asked to avoid the use of lotions or creams on their arms and to collect a sample of their own urine. During the 28-hour study period, subjects were asked to avoid bathing and to wear clothing that protected their arms during the day to minimize friction against their skin.

Test Applications and Observations

Liquid semen in 50-μL aliquots was placed on eight demarcated, ventral forearm locations of each volunteer. Fifty-microliter samples of urine were also applied to two areas on the forearms. One semen area and one urine area served as sites for the measurements of fluorescence decay, as described below. The other sites were reserved for sample collection for forensic analyses. During the 28-hour test period the same examiner (T.G.) held a WL (Mineralight UVL-56 *Blak Ray* Ultraviolet Lamp, Ultraviolet Products Inc, San Gabriel, Calif) over the forearms, and the fluorescence of semen and urine was recorded as either positive, faint, or negative. The pattern of fluorescence was recorded as even or irregular, and the color was noted as yellow-green or white.

Each subject had a WL reading performed at 15 minutes and 4, 7, 11, 24, and 28 hours after semen and urine application. At each interval, specimens were taken for forensic analyses by swabbing one of the semen areas with a cotton-tipped applicator moistened with sterile water. These swabs were air dried, frozen at 20°C, and transported to the laboratory.

Control swabs, taken from areas of the skin without semen or urine applications, were collected from 10 (91%) of the 11 subjects. Because the specificities of the forensic assays were known, only three (27%) of the 11 subjects had swabs of urine collected. These samples were similarly air dried and frozen for later analyses.

Laboratory Analyses

All forensic examiners were blind to the timing of the swab sample collection. The cotton portions of the swabs were extracted in isotonic Hepes buffer and centrifuged to separate the supernatant from the cellular debris; both fractions were frozen for later analyses.

Microscopy was performed using the cellular debris from the above procedure. A so-called Christmas tree stain[12] was used that stains sperm heads red and tail structures green. Results of microscopy were recorded as positive or negative depending on the presence or absence of spermatozoa. The ACP activity was assayed with a standard quantitative assay using p-nitrophenyl phosphate as a substrate.[9] The cutoff point for significance of ACP values was defined at 0.1 IU/mL since all skin control values were below this threshold.

The CIE assay for p30 allows semiquantitation of p30 levels and is sensitive to approximately 500 ng/mL.[13] The p30-CIE results were recorded as positive or negative. The p30-ELISA assay allows detection of p30 at concentrations as low as 2 ng/mL.[14] All skin control values registered less than the 2 ng/mL detection limit for the assay configuration used (Epichrome Immunometric Assay for prostatic antigen, Cetus Corp, Emeryville, Calif); therefore, this was used as our cutoff point below which test results were considered negative. (Although the assay kit used in this study is no longer commercially available, comparable assays for prostatic antigen p30 are available from Yang Laboratories, Seattle, Wash, and Hybritech, La Jolla, Calif.)

RESULTS

Ten (91%) of the 11 subjects had WL evaluations and swabs of dried semen taken at baseline and at the five specified intervals to 28 hours after semen application; the remaining subject missed one WL reading and swab collection 4 hours after application. One subject also missed one WL reading but was instructed to collect a swab sample per study protocol. In all, 65 samples were analyzed.

The visual appearance of semen and urine spots on the subjects' skin was assessed during the 28-hour study period. Semen spots initially appeared shiny or colloid-like, then turned flaky (72% of subjects had a flaky appearance 4 hours after semen application), and finally cleared over time. After 24 hours, the skin with semen appeared clear in nine subjects (82%). In contrast, skin with urine applications appeared clear throughout the study period.

WL Findings

The color of semen fluorescence was indistinguishable from the color of urine fluorescence throughout all periods. The pattern of semen fluorescence appeared irregular in texture, while the pattern of urine fluorescence was consistently homogeneous over time. As shown in Fig 1,

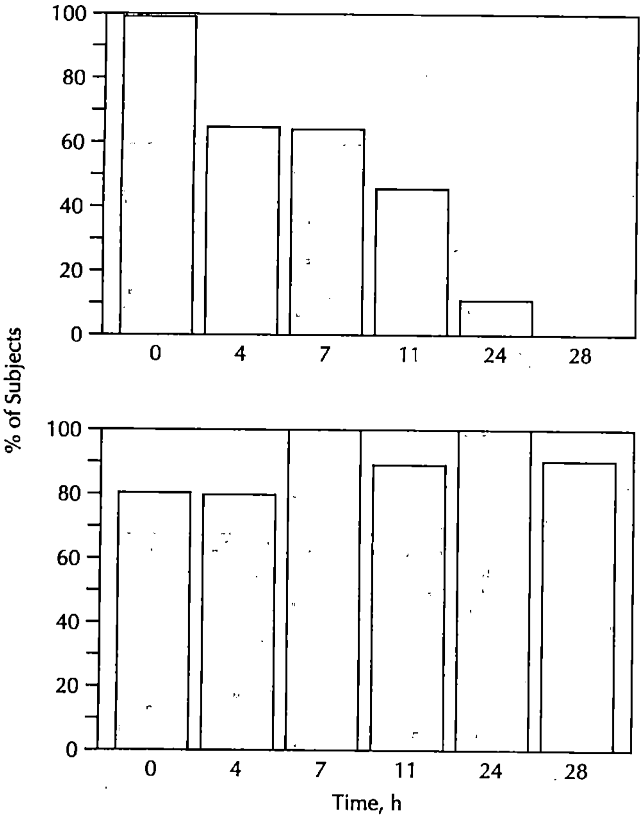

Fig 1.—*Top, Percentage of subjects with positive Wood's Lamp fluorescence of semen during a 28-hour period. Bottom, Percentage of subjects with positive Wood's Lamp fluorescence of urine during the same period.*

the intensity of semen fluorescence diminished dramatically over time. By 28 hours, six subjects (54%) exhibited faint semen fluorescence, but no subjects showed strongly positive fluorescence. In contrast, the fluorescence of 10 of the 11 urine spots remained strongly positive during the 28-hour period.

Forensic Analyses

The microscopic detection of sperm is generally considered to be the most sensitive and specific technique for semen detection.[5] By 28 hours, 55% of semen samples showed no microscopic evidence of the presence of sperm. The decline of ACP activity in the semen samples over time is shown in Fig 2. All samples were positive at the time of application, but with increasing time ACP values declined. By 28 hours, three (27%) of the 11 semen samples tested negative for ACP.

The p30 levels detected with CIE also declined with time. By 11 hours after semen application, four (36%) of the 11 samples had negative p30-CIE values, and at 28 hours seven (64%) of 11 samples had negative values. The p30-ELISA proved to be the most sensitive technique used (Fig 3). Before 28 hours no samples had negative test results. At 28 hours, only one (9%) of 11 samples had a p30 level that fell below the detection limit. Overall, the ELISA technique displayed greater sensitivity than did p30-CIE, microscopy, and ACP in detecting the presence of semen on skin. Sixty-three (97%) of 65 semen samples were found to be positive with the ELISA technique, while 47 (72%), 53 (82%), and 59 (91%) of the semen samples were

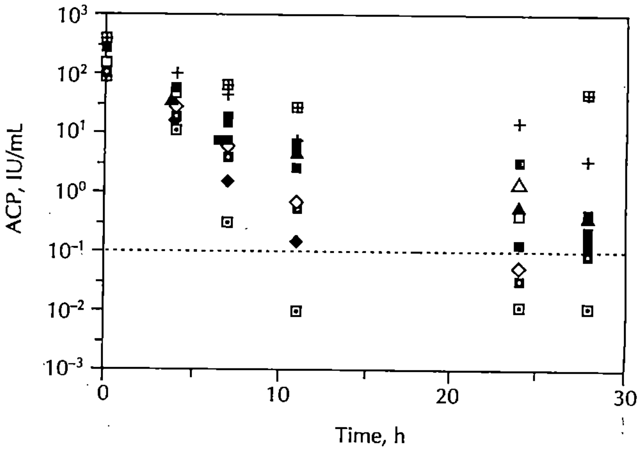

Fig 2.—*Acid phosphatase (ACP) concentrations (log base 10 scale). The broken line indicates the cutoff value below which a value is considered negative. Each symbol indicates a different subject.*

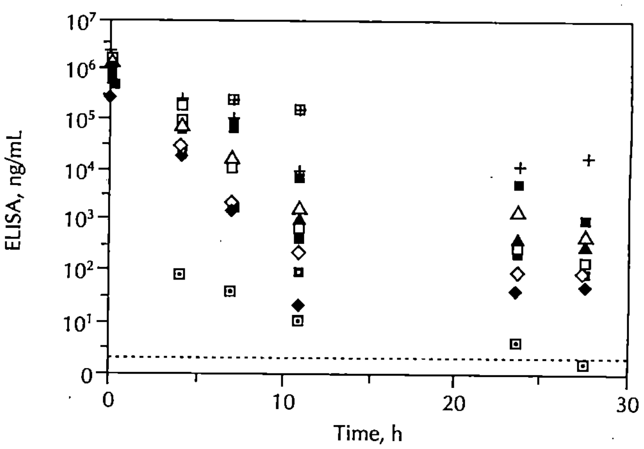

Fig 3.—*The prostatic protein p30 concentrations by enzyme-linked immunosorbent assay (ELISA) (log base 10 scale). The broken line indicates the cutoff value for a positive or negative value. Each symbol indicates a different subject.*

found to be positive with the p30-CIE technique, microscopy, and ACP, respectively.

Regardless of the results of semen fluorescence on skin, the p30-ELISA was more frequently positive than p30-CIE, microscopy, or ACP in detecting the presence of semen. The ELISA was 100% sensitive in detecting the presence of semen when no fluorescence was seen. This was in contrast with semen samples obtained from areas of no fluorescence evaluated with p30-CIE, microscopy, and ACP, which were positive only 34%, 56%, and 69% of the time, respectively.

Control swabs from areas of skin without urine or semen and from areas with urine only were analyzed with the ELISA technique. Results of these analyses were negative.

COMMENT

Despite study findings that the WL is nonspecific and only relatively sensitive for the detection of semen on body surfaces, it remains the only screening tool currently available to detect semen traces on the skin of child sexual assault victims. The timing of the clinical examination in relation to the alleged assault and the presence of fluorescent substances other than semen are important factors to consider when using the WL on a child or adult with suspected sexual abuse. As shown in this study, the fluorescence of semen on skin significantly diminished within 28 hours. In contrast, urine on skin remained fluorescent during the 28-hour test period and persisted until 80 hours in other test series. Since urine staining might be expected in the genital and thigh regions of children, positive WL observations must be interpreted with extreme caution. Overall, positive WL findings cannot be taken as definitive indications of the presence of semen because of the many substances that were shown to cause fluorescence. More important, negative WL findings should not be interpreted as indicating the absence of semen.

It is significant to note that the forensic tests were often capable of detecting semen when the WL fluorescence results were negative or inconclusive. The most sensitive of the four tests used in this study was the p30-ELISA technique. This assay has also been found to offer improved specificity and sensitivity in detecting semen in postcoital vaginal samples.[10] Although this ELISA assay is currently used in few US crime laboratories, this study suggests it may find particular application in the investigation of child sexual assault cases.

The rapid loss of detectable sperm in the test samples was somewhat surprising. This may be an artifact of the swabbing and extraction procedure. Alternatively, it may reflect the more rapid shedding or flaking of the bulk of the semen sample from the surface of skin. Overall, factors such as friction and rubbing on the sample area would be expected to accelerate semen loss from the skin surface. Other factors, such as chemical interactions on the skin surface, may also play a role. We acknowledge that the moisture, temperature, and chemistry of an adult's forearm skin may vary from the skin of a child's perineum; thus our findings might differ if children were used as subjects.

Recommendations for Using the WL and Collecting Samples

Despite its limitations, the WL allows clinicians to identify areas of skin with suspected semen, areas that may otherwise have gone unnoticed. Although the fluorescence of most samples faded by 28 hours, some areas maintained faint fluorescence. Because faint fluorescence may persist beyond the 28-hour period studied, the WL may be useful in cases in which a child presents within 72 hours of an assault; this follows the recommendation in the California Medical Protocol for Examination of Sexual Assault and Child Sexual Abuse Victims.[15]

During the WL examination, we recommend taking a swab of any white or yellow-green fluorescent areas on the patient's skin, paying particular attention to areas the patient identifies as sites of ejaculation. In cases selected for forensic analyses, swabs of the perineal area, inner thighs, and buttocks should be obtained even when the WL results are negative.

The entire area of skin in question should be wiped with a water-moistened swab, attempting to obtain as much material as possible on one swab. Rapid air drying, preferably with a drying box, and freezing are recommended to retard deterioration of the evidence material.[16,17] Repeated thawing and refreezing of samples is to be discouraged because of the potential for enzymatic and protein decay.

Recommendations for Forensic Analyses

Microscopic analysis for sperm and a chemical test for ACP and/or p30-CIE are routine in most crime laboratories. Our work demonstrates the importance of chemical testing in the absence of microscopic findings. Positive chemical findings may be obtained with any of the three chemical tests. A positive p30 assay may be considered conclusive evidence of the presence of semen. The p30-ELISA technique, if available, should be used since it is the most sensitive chemical test. Because of the lack of specificity of the ACP assay, a positive or negative ACP result warrants further analysis.

IMPLICATIONS

The results of this study are important for the development of clinical guidelines for use of the WL and the forensic methods studied here. Through additional clinical research, it is important to confirm the value of the WL as a screening tool and the value of forensic laboratory methods, particularly the p30-ELISA technique, as definitive, diagnostic tools for detecting semen traces on skin of acutely abused children. The strengths and limitations of each test used must be understood by the medical, forensic, and legal personnel involved in the investigation of child sexual abuse. With increasing knowledge, clinicians and forensic scientists will be able to assess child sexual abuse cases with more confidence and provide more convincing evidence for their use in legal proceedings.

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Home Visitation for Pregnant Women and Parents of Young Children

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• Many of the most pervasive, intractable, and costly problems faced by high-risk women and young children in our society today are a consequence of adverse maternal health-related behaviors (such as cigarette smoking, drinking, and drug use during pregnancy), dysfunctional infant care giving, and stressful environmental conditions that interfere with individual and family functioning. These problems include low birth weight, child abuse and neglect, childhood injuries, unintended and closely spaced pregnancy, and reduced economic self-sufficiency on the part of parents. Evidence is accumulating that these problems can be reduced with comprehensive programs of prenatal and infancy home visitation by nurses. While we are witnessing a renaissance of interest in home visitation as a means of addressing these problems, the recommendations of various health and human service advisory groups about the structure of proposed home-visitation initiatives are uncoordinated and frequently inconsistent with the empirical evidence. Home visitation is a promising strategy, but only when the program meets certain standards. The more successful programs contain the following: (1) a focus on families at greater need for the service, (2) the use of nurses who begin during pregnancy and follow the family at least through the second year of the child's life, (3) the promotion of positive health-related behaviors and qualities of infant care giving, and (4) provisions to reduce family stress by improving the social and physical environments in which families live.

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Prior to the 1970s community health nursing was an integral part of the US public health strategy to address the needs of at-risk children and their families. In the last 2 decades, such services have been reduced severely. Where home-visitation services have been provided, they have focused almost exclusively on pregnant women and children with identified health problems. Few home-visitation services have been devoted to prevention and health promotion.[1] In part, this is because third-party payers have been willing to reimburse for tangible services, such as long-term care of the elderly and disabled children, while they have shied away from disease prevention and health promotion. It did not help that early evaluations of home-visitation services were not promising.[2] Many of the early studies were difficult to interpret because the programs tested were not designed to address the full range of adverse circumstances that interfere with maternal health and care-giving behaviors. Where the programs were designed well, the evaluations fell short of the highest standards for field experimentation. In spite of the reticence of third-party payers to support preventive services and the equivocal results of early research, home visitation is once again being promoted as a means of preventing the death and damage of our most vulnerable children.[3-9]

The US Advisory Board on Child Abuse and Neglect[3,4] has declared child maltreatment a national emergency, has identified home visitation as the most promising method of addressing this problem, and has called for the development of a national home visitation program for all new parents. The National Commission to Prevent Infant Mortality[5,6] has included home-visitation as a central part of its strategy to improve the outcomes of pregnancy and reduce infant mortality and morbidity. The Public Health Service Expert Panel on the Content of Prenatal Care has recommended that home visitation be included as part of an augmented set of services for low-income, at-risk women.[7,8] The General Accounting Office[9] issued a report in 1990 encouraging Congress to increase their level of support for home-visitation services through expansion of Title XIX of the Social Security Act. At least five legislative initiatives currently before Congress include provisions for expanding federal support for home-visitation services. In the meantime, at least 24 states have recently begun to increase their support of home-visitation services through a variety of Medicaid service categories.[9]

This renewed interest in home visitation derives from an increased appreciation for prevention in all aspects of health as well as from a recent accumulation of scientifically credible evidence that home visitation can be an effective preventive intervention for women and children.[10] This report synthesizes the evidence on home visitation for pregnant women and parents of young children and examines the current legislative initiatives in light of that evidence. The findings from a randomized trial of prena-

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Services Provided in Each of the Four Treatment Groups

Services Provided	Treatment Group 1 (n=90)	2 (n=94)	3 (n=100)	4 (n=116)
Health and developmental screening at the child's 12th and 24th month of life	Yes	Yes	Yes	Yes
Free transportation to regular prenatal and well-child visits	No	Yes	Yes	Yes
Home visitation by a nurse during pregnancy	No	No	Yes	Yes
Home visitation by a nurse during the child's first 2 years of life	No	No	No	Yes

tal and infancy home visitation by nurses carried out in Elmira, NY,[11-13] have played a central role in focusing attention on home visitation as a promising preventive intervention, so its design and results are reviewed below. We also examined evidence from other randomized trials[10] and analyzed those findings in relation to the proposals of major advisory groups and current legislative initiatives.

THE ELMIRA STUDY

Problems Addressed by the Program

The nurse home-visitation program tested in the Elmira trial was based on the premise that many of the most pervasive, intractable, and costly health problems faced by high-risk women and young children in our society are a consequence of adverse maternal health-related behaviors (such as cigarette smoking, drinking, and drug use during pregnancy), dysfunctional infant care giving, and stressful environmental conditions that interfere with individual and family functioning.[14-16] These maternal and child health problems include the following: preterm delivery and low birth weight, the leading determinants of infant mortality in the United States[17]; child abuse and neglect, a condition that some believe has grown to a national emergency[3]; childhood injuries, the leading cause of death among children aged 1 to 14 years[18]; unintended and closely spaced subsequent pregnancies, a factor that reduces child health care and leads to the enmeshment of families in poverty[19,20]; and obstructed educational and occupational achievements on the part of parents, factors that reduce family economic resources and self-sufficiency and contribute to the intergenerational cycle of poverty.[21]

Setting

Elmira is a small city of about 40 000, located in a semirural county of about 100 000 residents in upstate New York. The community was beset with extremely difficult economic conditions during the period of the study. In 1980 it was rated the worst Standard Statistical area in the United States in terms of its economic conditions.[22] Moreover, from the early 1970s through the mid-1980s the community had the highest rates of reported and verified cases of child abuse and neglect in New York State.[23]

Sample

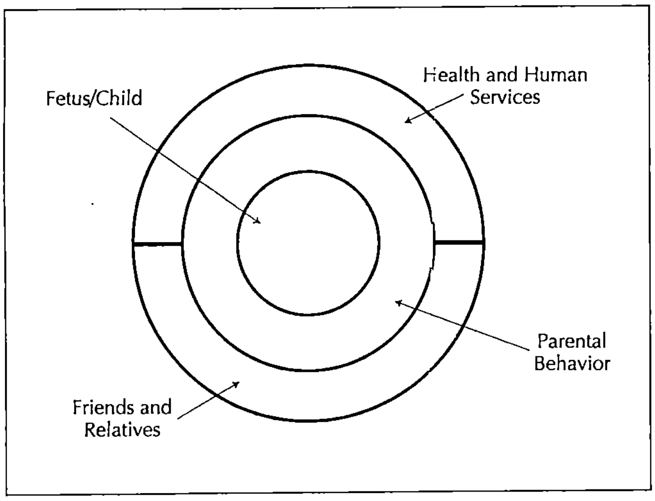
The investigators actively recruited into the study women who were having first children and who were at risk for poor pregnancy and child health outcomes by virtue of their being either poor, unmarried, or teenaged. Three hundred fifty-four (89%) of the 400 women registered were white, and all of the major findings reported apply to this group.

Treatment Conditions

The participating families were assigned at random to one of the four treatment conditions outlined in the Table. Families in treatment 1 received sensory and developmental screening for the children when they were aged 1 and 2 years. Children with potential problems were referred for further evaluation and treatment. Parents in treatment 2 received the screening services provided the first group as well as free transportation for prenatal and well-child care through a taxicab voucher system. Families in treatment 3 received the screening and transportation services plus prenatal home visitation by nurses. During pregnancy the nurses visited about once every 2 weeks. Those in treatment 4 received the screening, transportation, and prenatal home visitation plus postnatal home visitation through the child's second birthday. The nurses visited about once a week for the first 6 weeks after birth, and then visited on a schedule of diminishing frequency so that by the time the children were aged 2 years the nurses visited about once every 6 weeks.[11-13]

The Program

The Figure shows the broad conceptual framework that guided the design of the program and its evaluation. Epidemiologic evidence suggests that parental behavior is the most immediate, powerful, and potentially alterable influence on child health during pregnancy and the early years of the child's life.[24,25] In light of this evidence the nurses helped women improve their health-related behaviors, qualities of infant care giving, and personal development during their visits. They helped women do this by encouraging them to set small achievable goals and to use problem-solving methods to gain control over the difficulties they encountered. The women's accomplishments, in turn, enhanced their sense of competence in managing future problems. In an effort to create a home environment that was more conducive to optimal health behavior, the nurses involved other family members and friends in the pregnancy, birth, and early care of the child, and they linked families with other needed health and human services. They carried out this work in the context of establishing a long-lasting, therapeutic relationship with the mother and family by emphasizing individual and family strengths.[14-16]



Intervention model for high-risk families.

The Evaluation

The evaluation was designed to assess improvements in child health and development, parental health-related behaviors, qualities of infant care giving, social support, and use of community services from pregnancy through the child's fourth year of life, 2 years after the end of the program. Data were derived from interviews with parents, observations of parental behavior and conditions in the home, and reviews of medical and social service records. Except in a few cases in which families inadvertently disclosed that they were visited by nurses, all data-gathering staff were unaware of the families' treatment assignments.[11-13]

Improvement of Pregnancy Outcomes

In contrast to women in the comparison groups (treatments 1 and 2), women who received visits by a nurse during pregnancy (treatments 3 and 4) reduced the number of cigarettes smoked, improved the quality of their diets, had fewer kidney infections, experienced greater support from family members and friends, and made better use of the Special Supplemental Food Program for Women, Infants, and Children. The positive effects of the program on birth weight and length of gestation concentrated on two groups at risk for these problems: smokers visited by a nurse bore 75% fewer preterm infants, and young adolescents visited by a nurse bore infants who were 395 g heavier at birth than infants of their counterparts in the comparison group. While the effect of the program on the birth weight of infants born to very young adolescents was greater (given known determinants of birth weight) than predicted, the effect is consistent with the behavioral changes produced by the program and was particularly strong for those young adolescents who registered in the study before midgestation.[11]

Improvement of Care Giving

Among poor, unmarried teenagers, the incidence of state-verified cases of child abuse and neglect during the first 2 years after delivery was 19% in the comparison group (treatments 1 and 2) and 4% in the group that received both prenatal and infancy nurse visitation (treatment 4), an 80% reduction. These findings were corroborated by observations of the women's treatment of their children and conditions in the home. The homes of poor, unmarried teenagers visited by a nurse were filled with more educationally stimulating play materials, and the mothers used less punishment and restriction in interacting with their children. Moreover, during the second year of life (when childhood injuries increase), children visted by a nurse (irrespective of risk status) were seen in the emergency department 32% fewer times for any reason and 56% fewer times for injuries and ingestions than children not receiving visits by a nurse.[12]

Improvement of Maternal Personal Development

During the first 4 years after delivery, low-income, unmarried women in treatment 4 showed an 82% increase in the number of months they were employed, had 43% fewer subsequent pregnancies, and postponed the birth of a second child a mean of 12 months longer than did their counterparts in treatments 1 and 2.[13] The impact of the program on maternal care giving cannot be interpreted fully without acknowledging that high-risk women visited by nurses had fewer children for whom they were responsible.

Effect on Government Spending

An investment in this type of home-visitation program for low-income women and children can pay for itself (from the standpoint of government spending) by the time the children are aged 4 years. On average, the prenatal and postpartum program (treatment 4) costs about \$3200 for 2½ years of home visitation. Low-income women (those most likely to use government services) used \$3300 less in other government services during the first 4 years after delivery of their first child than did their low-income counterparts in the comparison group. About a third of the cost savings for low-income families came from the reduction in unintended subsequent pregnancies, and about 80% of the cost savings were concentrated in reduction in Aid to Families with Dependent Children and Food Stamp payments.[26] The cost savings may very well continue as the children grow older, but the families have not yet been followed up beyond the children's fourth year of life.

Generalizability of Findings

In interpreting the findings from the Elmira trial, it is important to keep in mind that the results were derived from one study carried out in a small, semirural community with a white sample in the late 1970s and early 1980s. We do not yet know whether these findings apply to minorities living in major urban areas in the 1990s. The Elmira trial is being replicated in Memphis, Tenn, with a sample of 1100 low-income black families to determine the generalizability of the findings. The report of program effects on the outcomes of pregnancy for the Memphis trial will be produced in the spring of 1993. Another way to determine the generalizability of the findings is to examine other randomized trials of home visitation for pregnant women and parents of young children and see whether the general pattern of results is the same.

Other Trials of Home Visitation

A recent review of all of the randomized trials of pregnancy and infancy home-visitation programs aimed at preventing health and developmental problems in pregnant women and young children showed that programs vary tremendously in terms of their objectives, target populations, structure, the background of the visitors, and their corresponding effectiveness. Some home-visitation programs simply do not work.[10] The more successful programs focus their services on families at greater need for the service and use nurses who visit frequently, beginning during pregnancy and continuing at least through the second year of the child's life. The nurses promote positive health-related behaviors and qualities of infant care giving, and reduce family stress by improving the social and physical environments in which families live. In other words, the programs are based on comprehensive service models.[10]

Policy Initiatives in Home Visitation

Few of the legislative initiatives currently before Congress or other home-visitation proposals contain all of the programmatic features necessary for program success. The US Advisory Board on Child Abuse and Neglect,[4] for example, calls for the development of a national home-visitation program using paraprofessional home visitors who begin following up families in the newborn period. Similarly, the National Commission to Prevent Infant Mortality[5,6] emphasizes paraprofessional programs with postnatal follow-up through the first year of life. Evidence from the Elmira study and other randomized trials suggests that the more successful programs use nurses who begin during pregnancy, follow up families through the second year of life, and focus their work on families at greatest need.[10-13]

While the US Advisory Board on Child Abuse and Neglect may be concerned about stigmatizing families unless the program is developed as a universal entitlement, the evidence suggests that scarce resources will be diluted, undermining the effectiveness of the initiative if it is made universally available. The viability of a nurse home-visitation initiative also has been questioned because of the nursing shortage, but evidence indicates that nursing school enrollments have increased in recent years and that the nursing shortage is declining (*The New York Times.* January 18, 1992:8).[27]

With the exception of a recent study in Baltimore, Md, of a single nonnurse home visitor who was able to reduce the incidence of hospitalizations and child maltreatment and improve health-care utilization in a sample of low-income parents,[28] there is little scientifically credible evidence from randomized trials of paraprofessional home visitation indicating that such programs can improve maternal or child outcomes of clinical importance. Moreover, there is wide variability in interpreting what constitutes a paraprofessional worker.

The Baltimore study tested a single college-educated home visitor who followed up families through the second year of the child's life using a multiproblem, comprehensive approach to working with families. Most of the proposals for paraprofessional home visitation call for community women to carry out this work with more limited objectives and for shorter durations. The efficacy of the more narrowly defined approaches using paraprofessionals simply is not well established. The evidence suggests that the full potential of home visitation will not be realized unless the program employs well-prepared visitors (nurses are best) who begin during pregnancy and continue to follow up families at least throughout the second year of the child's life.[10]

It is important to note that about a third of the cost savings realized in the Elmira trial came from the reduction in unintended subsequent pregnancies, and about 80% of the cost savings for low-income families were accounted for by the reduction in Aid to Families with Dependent Children and Food Stamp payments.[26] This finding emphasizes the importance of designing such programs with a broad multiproblem focus if they are to be economically viable. The multiproblem focus probably also adds to the power of such programs, in that improvements in one aspect of maternal or child functioning make it easier to facilitate improvements in other areas. Most of those programs currently proposed focus on single domains (eg, improvement of pregnancy outcome or reduction in child abuse) and thus fail in this regard.

The one home-visitation legislative initiative that comes closest to containing those programmatic features that show greatest promise is the Healthy Beginnings Act (HR 1244).[29] It calls for prenatal and infancy home visitation by a nurse that would continue at least through the child's second year of life. The program would be focused on those communities with the highest rates of infant mortality in the country, and the services would be based on a comprehensive model designed to address simultaneously a multitude of maternal and family needs. The bill also calls for continuous examination of these initiatives in the form of additional randomized trials. In spite of the difficulties encountered in carrying out randomized trials of complex interventions, they are especially important because we need to continuously refine our understanding of the extent to which such programs produce positive effects.

COMMENT

The recommendations and legislative initiatives reviewed here suggest that we may be on the brink of witnessing the development of a national home-visitation program for parents and young children. Because home-visitation programs vary so much in their design and corresponding effectiveness, considerable attention should be given to formulating an approach that is consistent with the evidence on which program features are most likely to produce program success. The direction that is set now will determine the structure and success of such a program for decades.

In light of the diverse home-visiting approaches being promoted, federal policymakers would be wise to convene a conference of representatives from the Infant Mortality Commission, the US Advisory Board on Child Abuse and Neglect, relevant members of the research community, and federal and state governments to forge an approach that makes sense in light of available evidence and resources. We must move quickly and carefully.

The US Advisory Board on Child Abuse and Neglect has observed that we are facing a national emergency because of the dissolution of adequate support for parents. They note that the ensuing abuse, neglect, and disability of our children ultimately endanger us all and pose a greater threat to our national security than any foreign enemy in our history.[3] Our children's future and the future of our society depend on our taking decisive action. We must embark on this journey, however, with full awareness that the course is still far from well marked, and that we may need to make midcourse corrections along the way.

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Zinc-Induced Copper Deficiency in an Infant

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• *Objective.*—To describe the case of a 13-month-old girl who developed copper deficiency as a result of excessive zinc gluconate ingestion.

Setting.—Tertiary care hospital in Syracuse, NY.

Interventions.—Cessation of zinc ingestion followed by intravenous and oral copper chloride therapy.

Measurements/Main Results.—Ingestion of zinc gluconate, 120 mg/d for 6 months, and thereafter 180 mg/d for 1 month, preceded the clinical presentation of listlessness, anemia, neutropenia, poor weight gain, abnormal sparse hair, and scorbuticlike bone changes. Findings on a bone marrow examination included ring sideroblasts and suggested copper deficiency. Plasma zinc level was 36.7 μmol/L, serum ceruloplasmin level was 20 mg/L, and serum copper level was undetectable. Clinical and laboratory abnormalities resolved shortly after initiation of copper therapy.

Conclusions.—This case demonstrates the reciprocal relationship of copper and zinc metabolism and exemplifies the important interrelationships of dietary trace minerals.

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Zinc is an essential trace element important for normal immune responses, wound healing, growth, and gonadal function.[1] Following the US Recommended Daily Allowance for zinc (0.5 mg per 420 kJ[2] or 15 mg/d for adults,[3] 3 to 5 mg/d for infants,[3,4] and 5 to 10 mg/d for children[3,5]) should ensure a positive zinc balance. Zinc intoxication may occur after inhalation, skin absorption, or accidental ingestion.[4] Acute effects of zinc intoxication may include lethargy, confusion, abdominal cramps, vomiting, and fever.[4,6] In adults, cases have been reported in which chronic toxic effects of zinc resulted in copper deficiency with secondary anemia and neutropenia.[1,7-10] There is one other reported case of excessive zinc ingestion and copper deficiency in a breast-fed infant.[11] In these cases, supplemental zinc was either administered in excess of the recommended dosages or taken inappropriately.

The reciprocal relationship of serum zinc and serum copper is well known. Zinc is often used in the treatment of excessive copper accumulation, as in Wilson's disease.[8] We describe the case of a 13-month-old girl who received approximately three to five times the recommended daily zinc requirements for a period of 7 months and who developed zinc-induced copper deficiency.

PATIENT REPORT

A 13-month-old white girl was referred to our institution for evaluation of a fever. She was in her usual state of health until 3 weeks before admission, when she developed a respiratory infection and was hospitalized at another institution. During her 8-day hospitalization, she was treated with bronchodilators, steroids, and antibiotics. While there, she developed oral thrush and *Candida* diaper dermatitis. Following discharge, and during the week before admission to our hospital, she had daily fevers, with temperatures reportedly as high as 40.8°C.

The product of a full-term, uncomplicated gestation, with birth weight at the 60th percentile, the patient's medical history was significant for recurrent otitis media. She was exclusively breast-fed and had received no immunizations.

The family history was significant for a 4-year-old sibling who had acrodermatitis enteropathica (diagnosed at age 8 months by skin biopsy) and a low serum zinc level (2.6 μmol/L). The mother and other siblings were prophylactically prescribed zinc gluconate supplements. In our patient, despite a normal baseline serum zinc level and no clinical signs of acrodermatitis enteropathica, oral zinc gluconate therapy was begun at age 6 months, 60 mg twice daily (16 mg/d of elemental zinc), and increased 1 month before this admission to 60 mg three times a day (24 mg/d of elemental zinc).

Physical examination on admission revealed a pale, listless girl with the following clinical values: rectal temperature, 39.7°C; pulse rate, 164 beats per minute; respirations, 52/min; and blood pressure, 103/68 mm Hg. The patient was 74 cm in length (between the 25th and 50th percentile for age), weighed 8.6 kg (between the 10th and 25th percentile for age), and her head circumference was 45 cm (at the 25th percentile for age). She had moderately enlarged tonsils covered with thick, white plaque. She had no lymphadenopathy. Her skin was normal. Her hair was thin and sparse. The results of the extremity examination were normal, with a full range of motion of all joints. The results of the remainder of the physical examination were also normal.

Initial laboratory evaluation revealed a hemoglobin level of 78 g/L, hematocrit of 0.24, platelet count of 327×10^9/L, and white blood cell count of 7.4×10^9/L. There were 0.84 lymphocytes, 0.11 neutrophils, and 0.05 monocytes. The patient's mean cell volume was 84.2 fL and red blood cell count was 2.85×10^{12}/L. The results of the examinations for electrolytes, glucose, and liver function were all normal. Serum iron was 16 μmol/L (nor-

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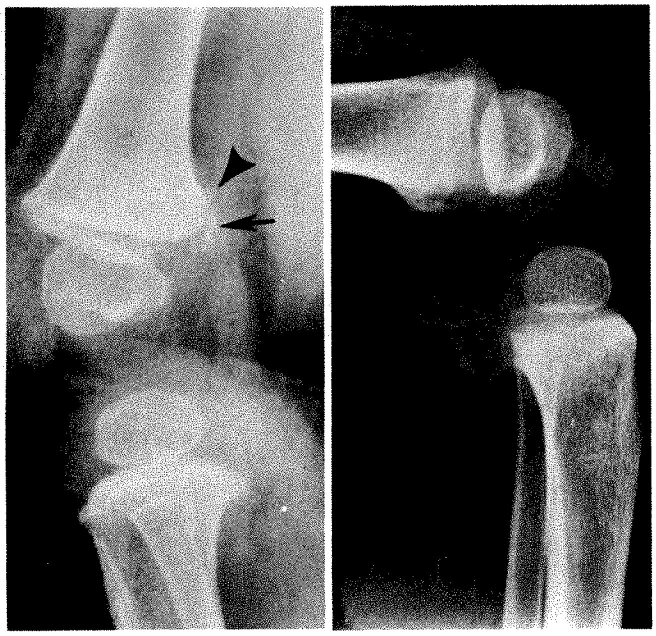
mal range, 8 to 24 µmol/L) and total iron-binding capacity was 53 µmol/L (normal range, 50 to 72 µmol/L). Erythrocyte sedimentation rate was 58 mm/h. A chest roentgenogram showed no abnormalities. A potassium hydroxide preparation of a throat swab demonstrated fungal elements. Bacterial cultures of blood, urine, and throat were negative. Nasopharyngeal and rectal swabs, performed on the day of admission, yielded adenovirus (type not reported).

All antibiotics were discontinued on admission. Intermittent fever was documented during the first few days of hospitalization. On day 3 of hospitalization, with a white blood cell count of 4.3×10^9/L, 0.86 lymphocytes, 0.07 neutrophils (absolute neutrophil count of 0.3×10^9/L), and fever, intravenous cefuroxime sodium was started. Subsequent complete blood cell counts consistently revealed neutropenia, relative lymphocytosis, and anemia. A bone marrow examination was performed on day 3 and revealed a normocellular marrow with mild granulocytic hyperplasia. There were vacuolated erythroid and myeloid cell precursors and ring sideroblasts. Neither subsequent viral nasopharyngeal cultures nor bone marrow viral culture yielded any growth.

Because these bone marrow findings suggested copper deficiency,[1] the patient's zinc supplement therapy was discontinued and plasma copper and zinc levels were obtained. The plasma zinc level was 36.7 µmol/L (normal range, 9.2 to 19.9 µmol/L), serum ceruloplasmin level was 20 mg/L (normal, 230 to 580 mg/L), and serum copper level was undetectable (limit of detection is 1.6 µmol/L). Maternal breast milk zinc level was 2.9 µmol/L of breast milk and copper level was 2.7 µmol/L of breast milk.



Left, Lateral roentgenogram of the knee before treatment reveals metaphyseal spur (arrowhead) and metaphyseal sickle-shaped fracture (arrow). Right, Lateral roentgenogram of the knee 2 months after treatment. There is healing of the metaphyseal abnormalities.

Roentgenograms of the knees revealed mild osteopenia of the bones, including the epiphysis. There were small metaphyseal spurs and sickle-shaped fractures at the distal femur (Figure).

A 4-day course of continuous infusion of intravenous copper chloride (600 µg/d [approximately 70 µg/kg]) was initiated. The patient was discharged home to be treated with copper chloride mixed in aromatic elixir, 200 µg three times a day. Subsequent white blood cell counts and plasma zinc, serum copper, and ceruloplasmin levels are listed in the Table. One month after beginning copper treatment, the patient's weight had increased to 9.6 kg, an increase of 1 kg since pretreatment. Roentgenographic findings had almost completely resolved (Figure). The copper solution was discontinued at 2 months after discharge. One year after discharge, the patient is asymptomatic with laboratory values as listed in the Table.

RESULTS

Although the medical indications for zinc therapy are abundant, the exact amount of dietary zinc that has a toxic effect and/or causes hypocupremia is not established. Acute toxic effects such as vomiting and diarrhea can result from ingestion of amounts exceeding 2 g.[5] Zinc-induced copper deficiency has been reported in adults taking doses of between 50 and 150 mg of elemental zinc per day.[8,9] In a previously reported case of a 4.5-kg exclusively breast-fed infant with acrodermatitis enteropathica, copper deficiency occurred after ingesting 30 mg of elemental zinc daily for 3 weeks.[11]

The metabolism of copper and zinc are linked and a reciprocal relationship is known to exist in both humans and experimental animals.[9] High dietary intake of zinc is thought to induce intracellular metal-binding proteins and metallothioneins in the gut mucosa.[2] With excessive zinc intake, these proteins bind to copper and decrease intestinal copper absorption.

The clinical findings of copper deficiency[12] include central nervous system abnormalities, anemia, neutropenia,[13] growth failure, pilus tortus (Menkes' kinky hair syndrome), and scorbuticlike bone changes.[14,15] On presentation, our patient exhibited listlessness, anemia, neutropenia, poor weight gain, clinically abnormal hair, and abnormal skeletal roentgenograms. The vacuolated normoblasts and ring sideroblasts, which were observed in the bone marrow, are indicators of copper deficiency but can also be seen in alcoholism, chloramphenicol toxic effects, and phenylketonuria.[1,16] The diagnosis of copper deficiency is supported not only by the bone marrow findings and the low serum copper and ceruloplasmin levels, but also by the resolution of the anemia and neutropenia, and improved clinical findings after administration of copper chloride. The role of adenovirus in causing the neutropenia is not clear in this case. Roent-

Laboratory Findings in Oral Copper Therapy

	White Blood Cell Count, $\times 10^9$/L	Hemoglobin, g/L	Reticulocyte Count, % of Red Blood Cells	Absolute Neutrophil Count	Zinc, µmol/L	Copper, µmol/L	Ceruloplasmin, mg/L
On admission	7.8	78	. . .	0.9×10^9/L	. . .	. . .	. . .
Before copper treatment	4.3	72	0.4	0.3×10^9/L	36.7	<1.6	20
After copper treatment was begun							
2 wk	6.6	111	6.2	1.8×10^9/L	33.7	8.2	270
2 mo	7.4	115	1.1	3.0×10^9/L	23.9	14.5	270
1 y	7.2	131	1.6	1.5×10^9/L	11.0	13.5	320

genographic findings in copper deficiency are similar to those of Menkes' kinky hair syndrome[12] as well as vitamin C deficiency.[14] Ascorbic acid requires copper for its synthesis, and absence of either causes defective collagen. After treatment with copper, the roentgenographic findings had almost completely resolved (Figure). Unfortunately, the hair was not examined microscopically and we were unable to document improvement after copper therapy.

Other acquired nutritional deficiencies of copper are rare, but can occur with hypoproteinemic states, in patients given total parenteral alimentation, and in premature infants.[1,17,18] Our patient did not receive total parenteral alimentation, was not premature, and did not have clinical or laboratory signs of protein-losing enteropathy, nephrotic syndrome, or other protein-depleted states. Copper deficiency may be congenital, as in Menkes' kinky hair syndrome.[12] Congenital copper deficiency is unlikely in this case since the patient had been neurologically normal until the recent development of listlessness. She also did not have the severe signs and symptoms that would be expected in congenital deficiency. In children with Menkes' kinky hair syndrome, treatment with copper does not reverse the abnormalities.[12]

The concentration of zinc and copper in the breast milk in our case were within the established normal range (greater than 6 months post partum).[2] Our patient had a dietary intake of copper that was limited to the copper in her mother's breast milk. Since the copper concentration in the breast milk was normal, it is unlikely that decreased copper intake contributed significantly to the copper deficiency. Had the infant been on a more general diet, there might have been enough copper ingested to offset the excess zinc.[19]

Low serum zinc is associated with retarded growth and delayed sexual development.[3,20] However, there is little evidence that either copper or zinc is clearly a growth-limiting factor. Our patient was failing to thrive, while zinc levels were high and weight gain was evident after copper treatment. Zinc toxic effects or copper deficiency may affect appetite. It is probable that her low weight was secondary to a decreased appetite and poor caloric intake.

COMMENT

This patient, a 13-month-old girl, who was administered zinc prophylactically, clearly demonstrates the reciprocal relationship of zinc and copper metabolism. It exemplifies the type of problem that can occur when interrelationships between trace minerals are disturbed. With chronic zinc intoxication, the patient developed signs, symptoms, and laboratory findings of copper deficiency. These findings all resolved with cessation of zinc supplementation and initiation of judicious copper therapy.

Aside from the medical uses of zinc, this trace mineral is often self-administered by adults to treat various ailments. This practice could result in clinical or subclinical copper deficiency. Although zinc is rarely prescribed for children, the physician should be aware of the possibility of parental administration of this mineral. Any child who is given zinc for medical or other reasons must have regular evaluations of serum copper and zinc levels.

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Measured vs Calculated Plasma Osmolality in Infants With Very Low Birth Weights

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• *Objective.*—To determine the relationship between measured serum osmolality (MsOsm) and calculated osmolality and to examine factors that may affect the osmolal gap.

***Research Design.*—Longitudinal cohort study.**

***Setting.*—Regional tertiary neonatal intensive care nursery in a university-affiliated hospital.**

***Patients.*—Sixty low-birth-weight infants (birth weight, 540 to 1500 g), studied daily during the first week of life.**

***Selection Procedure.*—Consecutive sample.**

***Interventions.*—None.**

***Measurements and Results.*—The MsOsm was significantly higher than the calculated osmolality for the first 6 days of life. The MsOsm was significantly higher during the first 6 days of life in infants with birth weights less than 1000 g than in those with birth weights greater than 1000 g, but the calculated osmolality was similar in both groups. Intraventricular hemorrhage, preservative additives in drugs, and packed red blood cell transfusions did not contribute significantly to osmolal gap or MsOsm. In 19 patients, peak MsOsm was greater than or equal to 320 mmol/kg (mean, 336±13 mmol/kg; calculated osmolality, 298±20 mmol/kg; osmolal gap, 38±19 mmol/kg). Six of these 19 patients died (all with birth weights <1000 g).**

***Conclusions.*—A significant proportion of patients with very low birth weights (mostly <1000 g) have large osmolal gaps and/or an MsOsm greater than 300 mmol/kg during the first week of life. The relationship between increased MsOsm in infants with very low birth weights and effective osmolality requires further study. Therapeutic intervention based solely on elevated MsOsm is ill advised.**

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The osmolality of a solution is a reflection of the number of molecules dissolved in a solvent. Osmolality is expressed as moles of solutes per kilogram of solvent, while osmolarity relates to the moles of solute per liter of solution. From the physical chemistry standpoint, the "osmolal anatomy" of body fluids is complex and includes a variety of substances whose contribution to the overall osmolality is diverse. In plasma, osmotic solutes include anions, cations, zwitterions (eg, amino acids), and nonionic substances. Under most clinical circumstances, plasma osmolality can be estimated by calculation from the measurements of sodium, urea, and glucose.[1] Measurement of plasma osmolality is, however, useful when the type and/or amount of substances of low molecular weight are abnormally present in plasma. In this situation, the difference between the measurement and calculation of plasma osmolality or osmolal gap can serve as an indirect method to demonstrate the existence of an abnormal solute.[2]

Previous studies on plasma osmolality in newborn infants yielded conflicting reports, attributable in part to differences in age, maturity, and feeding practices of the populations studied. Davis et al[3] found 16 of 60 term infants with plasma osmolality over 300 mmol/kg, while Dale et al[4] found that only three of 50 term infants had values in this range.

Davis et al[3] reported that the lack of correlation between serum sodium level and plasma osmolality during the first week of life precludes the use of sodium concentration as an indirect measure of plasma osmolality. Studies in preterm infants have shown plasma osmolality to be higher than in term infants.[5,6] Thomas[7] reported plasma hyperosmolality in preterm infants with intraventricular hemorrhage (IVH) that was not due to hypernatremia.

Several recent publications have heightened concern about the osmolality of preservative additives in preparations for parenteral administration given to preterm infants.[8-11] Propylene glycol has been the agent most commonly implicated in plasma hyperosmolality in these infants associated with a large osmolal gap.

We undertook a prospective study of a group of very-low-birth-weight (VLBW) infants during the first week of life to determine the relationship between measured serum osmolality (MsOsm) and calculated osmolality (calcOsm) and to examine factors that may affect the osmolal gap (the difference between MsOsm and calcOsm, also called "delta osmolality").

PATIENTS AND METHODS

Patient Population

The population consisted of 60 infants with birth weights of 1500 g or less who were admitted consecutively to the Eastern Oklahoma Perinatal Center, Tulsa.

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Table 1.—Calculated and Measured Osmolality in the Study Population

	Day						
	1	2	3	4	5	6	7
n	60	57	55	55	55	54	54
Mean (±SD) serum osmolality, mmol/kg							
Measured	290.9±15.1	301±18.9	305±17.2	300.2±16	297±11	294±11.5	288±42
Calculated	282±8.5	291±16.5	295±9.9	293±10.7	289±8	286±8.8	283±6.7
P	<.0001	<.001	<.001	<.01	<.0001	<.001	NS*

*Not significant.

The median birth weight was 1150 g (range, 540 to 1500 g), and the median gestational age was 28 weeks (range, 24 to 34 weeks). The distribution of Apgar scores was as follows: Apgar score of 3 or less, 23 patients at 1 minute and 7 patients at 5 minutes; score of 4 to 6, 25 patients at 1 minute and 17 patients at 5 minutes; and score greater than 6, 12 patients at 1 minute and 36 patients at 5 minutes. All infants enrolled in the study were maintained in a neutral environment in radiant warmers (OHMEDA Medical Systems, Atlanta, Ga) and received conventional ventilation and phototherapy treatment. A minimal handling protocol was applied to all infants.

Clinical Protocol

Infants were studied during the first week of life. Daily morning measurements for serum osmolality, sodium, potassium, total carbon dioxide, chloride, serum urea nitrogen, triglyceride, and plasma glucose levels were obtained. Osmolality was measured by means of an advanced micro-osmometer (TM, Advanced Instruments Inc, Needham Heights, Mass).

Urine was collected during the study period to determine 24-hour urine output and to measure urine osmolality. The study was approved by the Institutional Review Board of the hospital, and signed parental consent forms were obtained.

The patients were under the care of neonatologists who were not involved in the study. No attempt was made to standardize therapy. Cranial ultrasonography was performed on days 1, 3, and 5 of life with a high-resolution real-time sector scanner (RT3000, General Electric, Milwaukee, Wis). The ultrasound scans were interpreted by a sonographer who was unaware of the plasma osmolality.

The following measures were calculated and recorded daily for each patient: protein, fat, fluid, and energy intake, amounts (in milliosmols) of preservative additives present in drugs, and amount of sodium bicarbonate given by intravenous push. The amount in milliosmols of each component of the preservative solution (Adsol, Fenwal Laboratories, Round Lake, Ill) present in packed red blood cell transfusion was also calculated according to published estimates.[12] The serum anion gap was defined in millimoles per liter by the following formula: Anion Gap = (Sodium − Chloride + Bicarbonate).

Calculated Osmolality

The calcOsm was calculated by the following formula[1]:

CalcOsm (Millimoles per Kilogram of Water) =
2 × [Sodium (Millimoles per Liter)] +
[Glucose (Milligrams per Deciliter)/18] +
[Serum Urea Nitrogen (Milligrams per Deciliter)/2.8].

To improve precision, calcOsm was also estimated by the following formula[13]:

CalcOsm = 1.89(Sodium) + 1.38(Potassium) +
1.03[Urea (Millimoles per Liter)] +
1.08[Glucose (Millimoles per Liter)] + 7.45.

Unless otherwise noted, data on calcOsm are reported with the use of the first formula.

Statistical Analysis

Differences between calcOsm and MsOsm for the group as a whole and differences in calcOsm or sodium concentration between infants weighing less and more than 1000 g were tested for significance with unpaired Student's *t* test. The χ^2 test was used to compare proportions.

Repeated-measures analysis of variance for comparison of daily determinations of MsOsm and electrolyte levels was applied to subsets of infants with and without IVH.

Linear regression analysis was used to evaluate relationships between calcOsm and MsOsm. Pearson's correlation coefficient and multiple linear regression analysis were used to assess the relationship between MsOsm and other variables.

Data are expressed as mean±SD. Level of significance was $\alpha < .05$ for all statistical tests. No correction was made for multiple comparisons; hence, an increase in the risk of type I error cannot be discounted.[14] All reported *P* values are two tailed unless otherwise specified. Statistical analysis of all data was performed with Statistica (Statsoft Corp, Tulsa, Okla).

RESULTS

The 60 patients entered in the study ranged in birth weight (BW) between 540 and 1500 g. There were 23 infants with birth weights less than 1000 g and 37 with birth weights greater than 1000 g. Primary diagnoses were as follows: respiratory distress syndrome, 55 patients; Vater's syndrome, one; pulmonary hypoplasia, one; *Streptococcus* group B sepsis, one; and intrauterine growth retardation, two.

Six infants, all with birth weights less than 1000 g, died in the study period: three patients at age 1 day, two patients at age 2 days, and one infant at age 7 days. Causes of death were pulmonary hemorrhage, sepsis with shock, disseminated intravascular coagulation, air leak syndrome, respiratory failure, and pulmonary hypoplasia in one patient each. No IVH was present at autopsy in any of these infants.

Table 1 summarizes daily measurements of serum osmolality (MsOsm) and calcOsm for the group as a whole.

When data on serum osmolality for all 7 days were combined and stratified according to birth weight, infants with birth weights less than 1000 g (group A) had MsOsm values significantly higher than those in patients with birth weights greater than 1000 g (group B) (303±18 and 295±13 mmol/kg, respectively; $P < .001$). The calcOsm, however, was similar in both groups (289.5±13 and 288±9 mmol/kg, respectively). The anion gap for infants in group A was higher than that for those in group B (8.6±2.5 and 6.9±1.7 mmol/L, respectively; $P = .0113$).

Table 2 shows biochemical measurements and nutritional data in patients in groups A and B. The MsOsm was significantly higher in infants in group A than in infants

Table 2.—Osmolality, Blood Chemistry Findings, Nutritional Data, and Urine Data in Groups A (Birth Weight, <1000 g) and B (Birth Weight, >1000 g)*

	Day						
	1	2	3	4	5	6	7
Measured osmolality, mmol/kg							
Group A	297±20	310±21	311±17	302±22	303±12	297±12	301±18
Group B	286±7.2	296±15	302±16	299±12	290±10	292±10	291±12
P	NS	.006	.043	NS	.03	NS	0.029
Calculated osmolality, mmol/kg							
Group A	281±8.7	297±21	295±11	294±10	290±9	283±9	282±7
Group B	282±8.3	288±12	295±9	293±10	289±7	287±7	284±6
P	NS	.024	NS	NS	NS	NS	NS
Sodium, mmol/L							
Group A	135±4.6	140.8±6	141±5.6	140.3±5	139.1±4	135±5.5	135.1±4
Group B	137±4.1	138.5±5.5	142±5.3	141.4±5.4	139.6±3	139±4.0	137.1±3.9
P	NS	NS	NS	NS	NS	.024	.039
Glucose, mmol/L							
Group A	6.8±4.2	8.5±6.1	6.3±2.1	7.4±1.8	6.5±1.8	6.4±2	7.2±2.2
Group B	4.6±2	5.8±2.4	6.4±2.1	6.3±1.9	5.8±1.5	5.5±1.7	5.5±1.4
P	.006	0.013	NS	.069	NS	NS	.01
Serum urea nitrogen, mmol/L							
Group A	3.8±1.7	6.8±2.7	6.8±2.3	6.3±2.5	5.9±2.3	5.3±2.4	5.0±2.4
Group B	3.8±2.0	5.6±2.4	4.8±2.2	4.3±2.2	4.1±2.2	3.7±2	3.6±1.8
P	NS	NS	.0025	.002	.005	.006	.009
Total fluid intake, mL/kg per day							
Group A	141±39	163±51.8	188±44	207±60	205±52	207±56	206±52.6
Group B	93.9±20.2	119±26	134±27.8	145±33	151±36	155±33	152±24.8
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Energy, kJ/kg per day							
Group A	. . .	134±34	172±50	189±60	209±59	249±47	277±71
Group B	. . .	147±38	181±61	210±92	238±81	257±65	269±63
P	. . .	NS	NS	NS	NS	NS	NS
Protein intake, g/kg per day (N)							
Group A	. . .	0.5 (1)	0.64±0.22 (7)	0.73±0.30 (15)	1.12±0.41 (16)	1.43±0.52 (16)	1.84±0.67 (16)
Group B	. . .	0.5 (4)	0.57±0.18 (19)	0.77±0.27 (35)	1.18±0.33 (36)	1.6±0.41 (36)	2.0±0.46 (36)
Fat intake, g/kg per day (N)							
Group A	. . .	. . .	0.5 (2)	0.75 (2)	1.0±0.4 (3)	0.9±0.60 (6)	1.16±1.87 (9)
Group B	. . .	. . .	. . .	0.5 (5)	0.7±0.32 (11)	0.84±0.38 (16)	0.91±0.56 (23)
Urine output, mL/kg per hour							
Group A	2.38±1.4	4.7±2.1	5.15±2.27	5.37±2.4	4.92±1.92	5.6±1.7	5.6±2.4
Group B	2.39±1.33	4.0±1.8	4.24±1.22	4.38±1.4	5.41±1.4	4.02±1.23	3.8±1.18
P	NS	NS	NS	NS	NS	NS	<.001
Urine osmolality, mmol/kg							
Group A	279±95	233±94	286±97.4	245±77	266±88.2	269±89	212±105
Group B	166±52	202±83	247±87	240±83.7	230±73	232±87	231±98
P	<.0001	NS	NS	NS	NS	NS	NS

*Data are mean±SD. NS indicates not significant. *P* values are by one-tailed *t* test.

Table 3.—Patients With Measured Serum Osmolality Greater Than 300 mmol/kg

	Day						
	1	2	3	4	5	6	7
n	11	21	29	18	16	12	11
Mean (±SD) serum osmolality, mmol/kg							
Measured	314±18	320±16	316±15	316±12	310±11	310±6.7	315±13.8
Calculated	286±11	301±19	298±10	299±9.8	292±9.5	287±7.2	285±6.6
P	<.001	<.0001	<.001	<.001	<.001	<.0001	<.0001
No. of patients with sodium ≥150 mmol/L	0	1	2	2	0	0	0
No. of patients with sodium ≥145 mmol/L	0	9	14	2	4	3	0
No. of patients with plasma glucose ≥8.3 mmol/L	4	8	8	9	0	1	5
No. of patients with plasma glucose ≥13.9 mmol/L	2	2	0	0	0	0	0
No. of patients with potassium ≥6.8 mmol/L	1	0	0	0	0	0	0
No. of patients with serum urea nitrogen ≥10.7 mmol/L	0	3	1	0	1	1	1

in group B on each day, with the exception of days 4 and 6. Conversely, calcOsm was similar in both groups, except on day 2, when calcOsm in infants in group A was significantly higher than that in infants in group B. Plasma sodium concentration was similar in both groups during the first 5 days of life. Plasma glucose concentrations were higher in the patients with the lower birth weights on days 1, 2, 4, and 7. A few patients in this study developed a hyperosmolal state secondary to hypernatremia and hyperglycemia, previously reported in VLBW infants of less than 27 weeks of gestation.[15] In most instances, however, hyperglycemia was not severe enough to explain the degree of hyperosmolality, a fact reflected in the coexistence of large osmolal gaps. The serum urea nitrogen level was higher in infants in group A than in those in group B on days 3 through 7.

Osmolality and Sodium Concentrations in Infants With IVH

Intraventricular hemorrhage occurred in 10 (17%) of 60 patients. The distribution of severity according to the classification of Papile et al[16] was as follows: grade 1, five patients; grade 2, four; grade 3, two; and grade 4, two. The IVH was bilateral in three infants. Nine of 10 patients with IVH had a birth weight less than 1000 g. Daily MsOsm and sodium concentrations in these patients were compared with similar measurements in the remaining 14 infants in the study with birth weights less than 1000 g who did not have IVH. No statistically significant difference was found between these two groups.

Osmolal Gap

Osmolal gaps, calculated by the two formulas given earlier were highly correlated ($r = .98$, $P < .0001$). Since osmolal gap greater than 10 mmol/kg is considered abnormal, data above that value were included in the analysis. There were 132 and 131 values of osmolal gap that were greater than 10 mmol/kg with the first and second formulas, respectively. The corresponding means were 23.4±13.4 and 28.6±13.7 mmol/kg.

Patients With Osmolality Greater Than 300 mmol/kg

An MsOsm greater than 300 mmol/kg occurred in 118 of 385 determinations. Infants in group A had a significantly higher percentage of MsOsm measurements over 300 mmol/kg than did infants in group B (42% vs 24%; $P < .0001$). Table 3 gives MsOsm and calcOsm in study patients with MsOsm values greater than 300 mmol/kg. This table also shows that in 46% of the MsOsm determinations, plasma, sodium, glucose, potassium, serum urea nitrogen, and glucose plasma concentrations were within normal limits.

The subset of infants with serum osmolality greater than 320 mmol/kg was then analyzed. There were 19 patients in this group, and 13 (68%) of these patients had birth weights less than 1000 g. The mean MsOsm and calcOsm were 336±13 and 298±20 mmol/kg, respectively ($P < .01$). The osmolal gap was 38±19 mmol/kg. Five of these patients (28%), all with birth weights less than 1000 g, died.

The frequency distribution according to the number of determinations greater than 320 mmol/kg were as follows: one patient had four such determinations in 4 consecutive days and died; two patients had three in nonconsecutive days, and four patients had two (one in nonconsecutive days). There were 13 single determinations greater than 320 mmol/kg. In 16 (51.6%) of the 31 measurements of serum osmolality greater than 320 mmol/kg, the calcOsm was less than 300 mmol/kg. The corresponding figure in those patients who died was two of eight measurements.

Additives and Sodium Bicarbonate Intravenous Pushes

The amount of milliosmols of propylene glycol received by the study patients was insignificant. The highest amount was shown on day 1 (median, 2.4 mOsm/kg; range, 0.28 to 4.13 mOsm/kg) and progressively declined.

Most of the propylene glycol was present in the phenobarbital solution. The amount of milliosmols of additives infused with packed red blood cells was also highest on the first day (median, 2.2 mOsm/kg; range, 1.2 to 14 mOsm/kg) and decreased thereafter. A single infant received 14 mOsm/kg in multiple transfusions on the first day of life. Five of 60 patients received sodium bicarbonate by intravenous push. The amount of sodium bicarbonate given was insignificant and did not produce hyperosmolality. The highest amount was given on day 1 (median, 2.2 mOsm/kg; range, 2.2 to 12 mOsm/kg).

Correlations and Multiple Regression

When individual measurements in each patient were pooled, analysis of the derived patient data revealed that MsOsm was significantly, albeit weakly, correlated with plasma sodium level ($r=.56$, $P<.0001$), protein intake ($r=-.48$, $P<.001$), energy intake ($r=-.47$, $P<.001$), serum urea nitrogen level ($r=.45$, $P<.001$), anion gap ($r=.50$, $P<.001$), and glucose level ($r=.28$, $P<.05$). The correlation between MsOsm and birth weight was $r=-.40$ ($P<.02$). Because infants enrolled in the study were treated according to a minimal handling protocol, systematic daily weight data were available in only 32 of the 60 patients. In these patients, neither osmolality nor osmolal gap was correlated with maximum percentage weight loss.

The strongest predictors of MsOsm via multiple regression analysis were plasma sodium level ($\beta=.52$, $P<.0001$) and birth weight ($\beta=-.25$, $P<.05$).

COMMENT

Perturbations in serum or plasma osmolality typically parallel changes in the serum or plasma concentrations of sodium, glucose, or urea. Because osmolality may be calculated with acceptable accuracy by means of the measured concentrations of those solutes, measurement of serum osmolality is considered superfluous unless solutes of relatively low molecular weight unaccounted for by the standard formula are present in plasma in substantial amounts.

Overall, the present study demonstrated a significant proportion of patients having a larger than normal osmolal gap and of osmolality measurements greater than 300 mmol/kg, usually considered the upper limit of normal.[17]

Elevations of the osmolal gap can occur under two circumstances: (1) decrease in the aqueous phase of serum due to its displacement by abnormally large concentrations of lipids or proteins and (2) accumulation of endogenous osmols or the introduction of exogenous low-molecular-weight substances. In the former situation, calculated osmolality is low and the measured osmolality is normal, while in the latter, the measured osmolality is abnormally high.

The increased osmolal gap in our patients was not due to hyperlipidemia, while hyperproteinemia is not a consideration in low-birth-weight infants. The generation of endogenous osmols has been reported in renal failure, in shock[18] (mostly due to accumulation of lactic acid), and in dying patients.[19]

Renal failure was not a factor in producing large osmolal gaps in our patients. This is not surprising, since osmolal gaps have been reported mostly in patients with chronic rather than acute renal failure.[20] It is of interest that shock was present in the five patients with MsOsm greater than 320 mmol/kg who died. Hypotension was, however, not a consistent finding in patients with MsOsm greater than 300 mmol/kg or with osmolal gap greater than 10 mmol/kg. We did not obtain osmolality measurements in dying patients.

Reported instances of exogenous compounds producing large osmolal gaps in premature infants include propylene glycol in a parenteral multivitamin preparation, percutaneous absorption of alcohol, hyperosmolar contrast media, and enoximone infusion.[21]

The amount of milliosmols in the preservatives, including propylene glycol, and other low-molecular-weight substances, such as mannitol and sorbitol, received by the patients in our study group was insignificant and did not significantly contribute to the osmolal gap.

The previous and often quoted report by Thomas[7] of hyperosmolality in infants with IVH was not confirmed in our study. Thomas' study, which was performed before the development of cranial sonography, was confined to autopsy material. Infants who died with IVH had osmolality greater than 320 mmol/kg. Thomas postulated tissue breakdown secondary to marginal protein intake as the cause of hyperosmolality in his patients. Our patients with IVH had normal serum sodium concentrations, in agreement with Thomas' findings and a recent prospective in vivo study.[22]

The discrepancy between measured and calculated osmolality found in this study remains unexplained. Laboratory error, although possible, is unlikely, since the instrument used is considered to be accurate and measurements of osmolal gap in other patient populations in our setting were well within published values.[23] It has been suggested that the standard calculated methods underestimated the true osmolality of the sample.[24] Recalculation of the data by means of a "nearly accurate formula"[13] did not substantially change the frequency distribution of osmolal gap values.

We are thus led to postulate the existence of "extra" osmotically active substances in VLBW infants during the first week of life. The correlation between anion gap and MsOsm found in this study would suggest that an anion may have contributed to the osmolal gap. We did not measure lactate concentrations. Furthermore, the anion gap has been found to be an insensitive screen to detect hyperlactatemia.[25] Thus, an increase in lactate concentrations cannot be ruled out.

Like osmolality, the anion gap is a complex multivariable equation that is commonly oversimplified by using only serum sodium, chloride, and bicarbonate concentrations in its estimation.

The concentration and/or charge of serum proteins (especially albumin) can affect both the anion gap[26] and serum osmolality. Divalent ions are partially bound to plasma albumin.[27] It is known that serum proteins in the newborn infant bind xenobiotics to a lesser extent than do proteins in adults.[28] Since osmolality depends on the number of particles in solution, it is theoretically possible that a decrease in the binding of divalent ions to plasma proteins in low-birth-weight infants could result in an increase in MsOsm. There are, however, no experimental studies addressing this postulation.

All infants in this investigation received amino acid preparations as part of parenteral nutrition during the study period. It is known that the concentration of certain plasma amino acids increases markedly during parenteral nutrition of newborn infants.[29,30] Furthermore, an increase in serum osmolality has been observed in anuric infants receiving a parenteral amino acid preparation.[31] It is tempting to speculate that high plasma levels of amino acids resulting from the use of parenteral nutrition, coupled with impaired liver metabolism in sick VLBW infants,[32] may be a source of unmeasured milliosmols.

Finally, the negative correlation, albeit weak, between energy and protein intake and MsOsm together with increased serum urea nitrogen levels in group A infants suggests a possible role for products of tissue catabolism. At any rate, the existence of extra osmotically active substances in the plasma of VLBW infants remains an unproved possibility. A systematic search for these substances could answer the question of whether they actually exist and, if so, their clinical significance.

It is important to stress that an increased extracellular osmolality will result in redistribution of water between intracellular and extracellular compartments only if the responsible substances do not readily enter the cells. In this regard, measurements of plasma osmolality bear no relation to effective osmolality. Biologic function depends on the latter, which can only be inferred from the concentrations of sodium, glucose, and any other compound present in the plasma that do not readily enter the cells. Thus, therapeutic interventions based solely on the measurement of plasma osmolality are unwarranted.

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Acid Peptic Disease in Children With Type I Diabetes Mellitus

A Complicating Relationship

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• **Objective.**—To determine the prevalence of acid peptic disease among pediatric patients with insulin-dependent diabetes mellitus and to study the effects of acid peptic disease on treatment of insulin-dependent diabetes mellitus.

Design.—Inception cohort and matched case-control study, with a data set derived from patient and parent interviews and inpatient and outpatient chart reviews.

Setting.—LeBonheur Children's Medical Center, a university-affiliated hospital in Memphis, Tenn.

Participants.—Thirty-one patients with insulin-dependent diabetes mellitus who presented with multiple episodes of symptoms of acid peptic disease were examined by endoscopy. Thirty-one control patients with insulin-dependent diabetes mellitus and transient or no gastrointestinal complaints were matched for age, gender, race, and duration of diabetes.

Measurements.—Glycosylated hemoglobin levels, stature, frequency of hospital admissions, and parental history of acid peptic disease.

Results.—Acid peptic disease occurred with a prevalence of 7% in our population of pediatric patients with insulin-dependent diabetes mellitus. Major endoscopic findings included gastritis confirmed by upper gastrointestinal biopsy (94%), bile staining of gastric mucosa (58%), and bile pooling (52%). Patients with acid peptic disease demonstrated shorter stature, greater frequency of hospital admissions, and greater prevalence of parental acid peptic disease by history than those of controls. In the 18 months following acid peptic disease therapy, hospital admissions for diabetes-related problems decreased by 50%.

Conclusions.—Acid peptic disease is an underrecognized complicating factor in the treatment of diabetes. Clinical suspicion is necessary to offset compromised diabetes control, compliance to treatment regimens, and/or growth expectations associated with this disease.

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Acid peptic disease is an inflammatory condition involving the upper gastrointestinal tract, sometimes associated with erosions and ulcers. A spectrum of symptoms, including abdominal or substernal pain, early satiety, abdominal bloating, nausea, and vomiting may be present. Symptoms usually subside following treatment with histamine receptor blockers, antacids, omeprazole, and sucralfate; however, recurrence of symptoms is common.

Little is known about the incidence of acid peptic disease in children,[1-4] and an association of gastrointestinal problems with type I diabetes mellitus in children[5] has not been recognized. In a 1985 review, Byrne[6] reported that the number of newly diagnosed cases of primary peptic ulcer disease in children appeared to be increasing. However, he was not able to discern whether this increase was real or secondary to improved diagnostic techniques. We have identified a large number of patients with symptoms suggesting acid peptic disease (7%) in our large population of pediatric patients with diabetes. When the first few patients were diagnosed by endoscopy as having acid peptic disease, we systematically canvassed patients at their next clinic visit about gastrointestinal problems and reviewed their medical records, noting hemoglobin A_{1c} concentrations, incidence of hospitalizations, and growth variables. We analyzed these data to answer the following questions: (1) Is acid peptic disease associated with poor diabetes control, as evidenced by elevated glycosylated hemoglobin (HbA_{1c}) levels and/or episodes of diabetic ketoacidosis? (2) Is acid peptic disease associated with impaired growth in children with diabetes mellitus? (3) Does treatment of gastrointestinal symptoms improve diabetes control? (4) Are certain children with diabetes predisposed to the development of acid peptic disease?

PATIENTS AND METHODS

From 1984 to 1986, 429 patients with insulin-dependent diabetes mellitus (IDDM) were screened during quarterly clinic visits for symptoms suggestive of acid peptic disease. Although some patients were identified by voicing specific complaints, both the child and parents were questioned regarding occurrences of nausea, abdominal pain, early satiety, vomiting, substernal pain, abdominal bloating, burning pain, morning fullness, constipation, epigastric pain, dysphagia, and diarrhea. The child was examined for abdominal tenderness, abdominal distention, and hepatomegaly. Patients and parents consented to routine care and surveillance and assented to routine epide-

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Table 1.—Patient Characteristics[*]

	Patients With IDDM and Acid Peptic Disease	Control Patients With IDDM
No.	31	31
Mean (±SD) age, y[†]	14.2±3.9	14.2±3.9
Mean (±SD) duration of IDDM	6.2±4.5	6.4±3.9
Male/female, No.	16/15	16/15
White/black, No.	22/9	22/9

[*] IDDM indicates insulin-dependent diabetes mellitus.

[†] Ages ranged from 5 to 19 years; five patients were aged 10 years or younger, 17 were aged 11 to 15 years, and nine were aged 16 years or older.

miologic inquiry and anthropometric testing. Patients (n=31) who demonstrated multiple episodes of symptoms persisting for at least a month were chosen for further evaluation by endoscopic examination during a 15-month period. This group of patients ranged in age from 5 to 19 years (mean age, 14.2 years). Patients who experienced transient gastrointestinal symptoms (lasting from a few hours to a few days and thereafter disappearing) and probably associated with viral infection or overeating were not examined by endoscopy. In some cases, symptoms preceded diagnosis by at least 6 months due to our reluctance to examine by endoscopy patients without multiple complaints and episodes of upper gastrointestinal symptoms. Thirty-one control patients with IDDM, but with transient or no gastrointestinal complaints, were chosen retrospectively from our patient population and matched for age, diabetes duration, gender, and race with patients with IDDM and symptoms suggesting acid peptic disease (Table 1). This pool of 429 patients from which patients with IDDM exhibiting acid peptic disease and control patients with IDDM were chosen included more than 90% of pediatric patients with IDDM in the Memphis metropolitan area and all patients with type I diabetes under long-term care in our pediatric diabetes clinic at the initiation of this study. None of the 62 patients in this study were chronic users of aspirin tablets or other nonsteroidal anti-inflammatory agents.

If a history and physical examination led to a preliminary diagnosis of acid peptic disease, a complete blood cell count and erythrocyte sedimentation rate were performed, followed by endoscopy. Esophagogastroduodenoscopy was performed with an Olympus XP10 endoscope with an Olympus CLE-4U cold light supply (Olympus Endoscopic Manufacturing Company, Japan). Patients were sedated with intravenous diazepam and meperidine hydrochloride, and their throats were sprayed with a topical anesthetic. After a 12-hour fast, endoscopy was performed. When food was found in the stomach, a dietary history was conducted to determine when the food was consumed. Six to eight biopsy specimens from the antrum, body of the stomach, duodenum, and occasionally the esophagus were obtained from 27 patients whose endoscopic examination results were suggestive of acid peptic disease. The remaining four patients with IDDM exhibiting such disease did not undergo biopsy due to technical difficulties (eg, agitation); regardless, the results of their endoscopic examinations did not differ from those in the group that underwent biopsy. For ethical reasons, we did not perform endoscopic examinations or biopsies on control patients with IDDM. Neither gastric emptying studies, esophageal motility studies, nor gastrointestinal roentgenography was performed. Mucosal biopsy specimens and standard pathologic criteria were used to establish histologic diagnoses of gastritis. All gastric biopsy specimens were stained using Steiner stain and searched for *Helicobacter pyloris*.

Gastritis or duodenitis was diagnosed clinically when there was definite redness, with superficial erosions of the gastric mucosa, ulcers (large erosions greater than 2 mm in width), or nodularity. A diagnosis of esophagitis was made when the esophagus was found to have marked redness, with linear erosions extending up from the squamocolumnar junction, large edematous folds, bile staining, or prolapsed lower esophageal sphincter. Gastric fold nodularity, bile staining (bile discoloration of the gastric mucosa), and bile pooling (90 to 240 mL residual bile-containing liquid in the stomach) were noted.

Outpatient evaluations were obtained at 3- to 4-month intervals. Medical records covering up to 18 months before diagnosis of acid peptic disease and up to 18 months following the beginning of therapy were analyzed. Comparable data were collected for each control patient. Data were compiled for HbA_{1c}, height, weight, Tanner pubertal stage, insulin dosage, number of insulin reactions, use of insulin pump, transient hepatomegaly, number of hospital admissions and emergency room visits, and response to treatment of acid peptic disease. Parental history of acid peptic disease was obtained by interviewing the parents. Information on parental height was obtained by questionnaire.

Glycosylated hemoglobin levels were determined by cation exchange chromatography (Bio-Rad, Richmond, Calif). Normal HbA_{1c} values for our nondiabetic pediatric patients ranged from 3.03% to 7.35%. Height percentiles were estimated from growth charts of the National Center for Health Statistics.[7]

Therapy for acid peptic disease varied depending on its severity and response to therapy. The typical patient was treated with histamine receptor antagonists, antacids, and diet restrictions for 2 months. Either cimetidine hydrochloride (in a dose of 10 to 20 mg/kg per day in four doses) or ranitidine hydrochloride (in a dose of 4 mg/kg per day in two doses) was used most frequently. Sucralfate was occasionally used either alone or with histamine receptor blockers. Sucralfate was favored if bile staining of gastric mucosa was present and was administered in a dose of 1 g before meals and at bedtime. Metoclopramide hydrochloride (in a dose of 0.3 to 0.5 mg/kg per day in three or four doses) was used in cases where patients reported symptoms of persistent nausea, vomiting, morning fullness, early satiety, and bloating. An avoidance of tomato products, citrus juices, and caffeinated beverages was recommended. Patients were also advised against the use of nonsteroidal anti-inflammatory drugs such as aspirin tablets.

RESULTS

Approximately 7% (or 31) of our pediatric patients with type I diabetes had acid peptic disease. Twenty-seven of these patients were found to have acid peptic disease during outpatient endoscopic examinations; the remaining four, who experienced multiple episodes of gastrointestinal symptoms, were diagnosed during hospitalization for treatment of diabetic ketoacidosis. More than 50% of the patients with acid peptic disease (Fig 1) had a recurrence of nausea, early satiety, substernal pain, and abdominal pain with or without tenderness in the epigastric area. However, two patients with severe acid peptic disease atypically presented with persistent abdominal bloating or morning fullness only. Both complete blood cell counts and erythrocyte sedimentation rates were normal for patients with IDDM and symptoms of acid peptic disease. In the control group, there were no multiple episodes of symptoms suggestive of gastrointestinal disease.

Endoscopy revealed inflammation of the stomach in 94% of the patients (Fig 2). More than half of the patients had bile staining of the gastric mucosa and bile pooling. Eleven of the 31 patients had retained food consumed 12 to 48 hours before examination. Ulcers and/or erosions were noted in 48% of the patients. Reflux esophagitis and duodenitis were found in a few patients. Histopathologic evidence of gastric biopsy corresponded with endoscopic observation in 25 of the 27 patients who had undergone

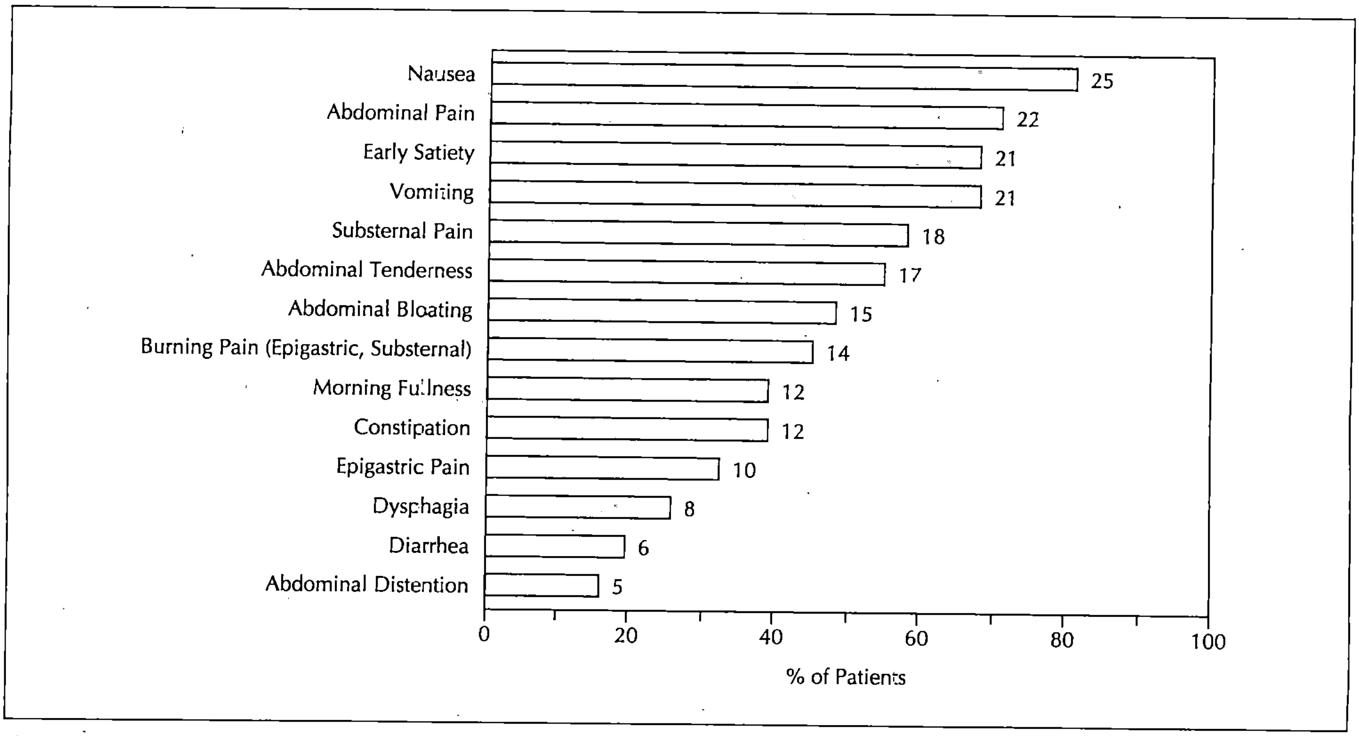

Fig 1.—*Presenting signs and symptoms of patients with insulin-dependent diabetes mellitus and acid peptic disease. The number of patients is indicated beside each bar.*

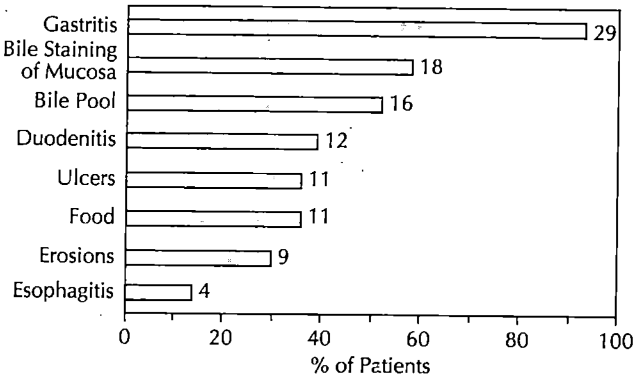

Fig 2.—*Endoscopic findings in patients with insulin-dependent diabetes mellitus and acid peptic disease. The number of patients is indicated beside each bar.*

biopsy. The severity of acid peptic disease varied from localized esophagitis, gastritis, and/or duodenitis to extensive bleeding ulcers and erosions. At endoscopic examination, gastritis was diagnosed clinically when there was notable redness accompanied by nodularity, ulcers, or erosions. Biopsy specimens were obtained from 27 patients. The remaining four patients with IDDM and symptoms of acid peptic disease did not undergo biopsy due to technical difficulties (eg, agitation), but their endoscopic examination results did not differ from those in the group that underwent biopsy. Mucosal biopsy specimens and application of standard pathologic criteria were used to establish a histologic diagnosis of gastritis. In one patient, histologic evidence of gastritis was seen where no abnormality was noted on endoscopic examination. In this group of patients, none was found to have histologic evidence of *Helicobacter pyloris*.

At diagnosis of acid peptic disease, the mean HbA_{1c} level of patients with acid peptic disease was slightly higher than that of the control patients, but the difference was not statistically significant according to a paired *t* test (Table 2). Twelve months after initial treatment for acid peptic disease, the mean HbA_{1c} level of patients with acid peptic disease was the same as that of the control group.

Nearly half (48%) of patients with acid peptic disease were in the lowest quartile of the expected height percentiles (Fig 3). Analysis by χ^2 demonstrated that height quartile distribution departed from the expected distribution (observed, $\chi^2=9.30$; $.025<P<.05$ with 3 *df*). The height distribution of matched control patients was normal ($\chi^2=2.03$). Thus, there is a statistically significant association between acid peptic disease and growth failure. The mean height percentile for patients with acid peptic disease was 37%, and that for controls was 49%. Tanner pubertal stages of the acid peptic disease group and the control group did not differ during the period studied and typically were normal for the range of chronological ages. Mean insulin dosage before and after treatment was similar between the two groups (Table 2), although five patients with acid peptic disease required insulin infusion pumps, while no control patients required insulin pump therapy. During this study, insulin infusion pumps were used only for the patients whose IDDM was most difficult to control. Ten of the acid peptic disease group and 12 of the control group had one or more insulin reactions varying from disorientation to loss of consciousness or seizures during the 36-month period analyzed.

Twenty-two patients with acid peptic disease had 78 hospitalizations in the 18 months before diagnosis. Sixteen patients had one to four admissions, and six had five or more admissions (Fig 4). Diabetic ketoacidosis or uncontrolled diabetes accounted for 64 (82%) of the hospitalizations. There were five hospitalizations (involving five patients) for gastritis, abdominal pain, or transient

Table 2.—Clinical Measurements of Children With Insulin-Dependent Diabetes Mellitus (IDDM)*

	Patients With IDDM and Acid Peptic Disease (n=31)		Control Patients With IDDM (n=31)	
	At Diagnosis	After Treatment	At Inception of Study	At End of Study
HbA_{1c}, %	9.3±3.1	8.4±1.7	8.2±1.5	8.3±1.6
Height, cm	149±16	155.8±12	154.9±16	159.8±13.5
Weight, kg	49.6±16	52.8±14	50.1±16	55.5±17.1
Insulin, U/kg per day	1.06±0.46	1.08±0.31	1.08±0.35	1.10±0.31

*Values are expressed as mean±SD.

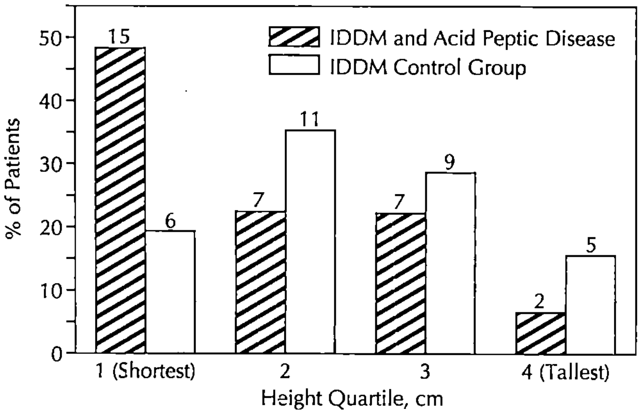

Fig 3.—*Quartile height distribution of patients with insulin-dependent diabetes mellitus (IDDM) and acid peptic disease and control patients with IDDM. On the abscissa, 1 indicates all the patients ranked in the lowest 25th percentile; 2, the 26th through 50th percentile; 3, the 51st through 75th percentile; and 4, the 76th through 100th percentile. The number of patients is indicated above each bar.*

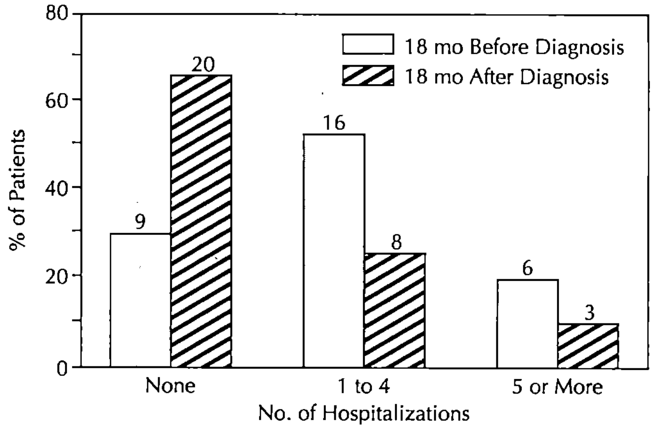

Fig 4.—*The number of patients who did not require hospitalization following treatment of acid peptic disease more than doubled. Matched control patients with insulin-dependent diabetes mellitus had few hospitalizations. The number of patients is indicated above each bar.*

hepatomegaly. The remaining four admissions were for treatment of infectious conditions. During the 18 months following diagnosis of acid peptic disease, both the number of patients hospitalized and the frequency of hospitalization decreased dramatically, with 11 patients undergoing 36 hospital admissions (Fig 4). Patients in the control group had considerably fewer hospitalizations. In the interval corresponding to the 18 months before acid peptic disease diagnosis, six control patients had six admissions; during the 18 months following diagnosis, two patients had four admissions.

The reduction in hospitalizations was accompanied by a slight reduction in the number of emergency room visits not leading to hospitalization. In the 18 months before acid peptic disease diagnosis, eight patients had 23 emergency room visits, while during the 18 months following diagnosis, nine patients had 18 such visits. During the entire 36 months, six control patients had eight emergency room visits. The majority of the emergency room visits by patients with acid peptic disease were related to uncontrolled diabetes. Two visits by members of the control group were for insulin reactions, while the remaining visits were not diabetes related.

Transient hepatomegaly not associated with significant elevation of liver function test results was found in five patients with acid peptic disease. One of these patients underwent biopsy and was found to have a fatty liver. None of the patients in the control group experienced hepatomegaly during the 36-month study period.

A parental history of acid peptic disease was reported for 15 patients with acid peptic disease. In three of these cases, both parents were affected. Seven patients in the control group had one parent who reported acid peptic disease ($P = .062$). Since there were no significant differences between the heights (expressed as mean±SD) of the parents of children with acid peptic disease (21 fathers, 178±9.2 cm; 21 mothers, 163±4.6 cm) and parents of control patients (14 fathers, 173±22.4 cm; 15 mothers, 166±7.7 cm), it is unlikely that the shorter stature of a disproportionate number of the patients with acid peptic disease was familial.

Following institution of therapy with antacids (n=18), ranitidine (n=18) or cimetidine (n=13), metoclopramide (n=21), and/or sucralfate (n=8) when indicated, all patients improved. Typically, treatment was tapered after approximately 1 month and discontinued after 2 months. Following discontinuation of drug therapy, recurrence of symptoms was common, and reinstitution of drug therapy was frequently needed. When symptoms recurred, chronic treatment consisted of histamine receptor blockers and antacids as needed to relieve pain. Some patients continued taking metoclopramide for persistent symptoms of nausea, vomiting, morning fullness, early satiety, and bloating. At 12 to 18 months after institution of drug therapy, seven of the 31 patients were asymptomatic and did not require medication, while the remaining 24 required continuing medication.

COMMENT

Until the advent of fiberoptic endoscopy in the 1970s, diagnosis of acid peptic disease in children was very difficult.[8] There is still little agreement concerning the incidence of the disease in children, although it is typically regarded as low.[1,9] Our data suggest that children and adolescents with IDDM are at risk of developing acid peptic disease. Factors that may play a causative role have not been delineated. However, it appears that positive parental history, short stature, and frequent hospitalization are more common among patients with IDDM and acid peptic disease than among other patients with IDDM.

It is not clear whether acid peptic disease made the diabetes worse or individuals with severe diabetes were more prone to acid peptic disease. Although we believe that children with uncontrolled diabetes are at greater risk of developing acid peptic disease, one third of both the acid peptic disease and control groups had excellent diabetes control as evidenced by HbA_{1c} values of less than 7%. Even mild hyperglycemia (blood glucose level of 7.8 mmol/L) may impair gastric motility in healthy adult volunteers.[10] Thus, it is possible that the chronic intermittent hyperglycemia typical in IDDM might lead to the duodenogastric reflux of bile and contribute to subsequent development of acid peptic disease. If one or both parents report acid peptic disease, the child with diabetes appears to be predisposed to the development of acid peptic disease.

As demonstrated in part by the higher incidence of diabetes-related hospitalizations, IDDM is more difficult to control in patients with acid peptic disease. Delayed gastric emptying may lead to inadequate diabetes control. The need of insulin pump therapy by five of 31 patients with IDDM and acid peptic disease and the occasional finding of transient hepatomegaly in this group is additional evidence of poor diabetes control. Furthermore, early satiety, nausea, and vomiting lead to reluctance on the part of the patient to consume the requisite calories at specific intervals, usually three meals and three snacks. Abdominal pain may also cause overeating to relieve symptoms. Counterregulatory hormones, such as epinephrine and cortisol, may be increased by the abdominal pain and gastrointestinal inflammation of acid peptic disease. Hyperglycemia irrespective of the cause can induce insulin resistance.[11] Hyperglycemia can also lead to loss of excessive fluid and electrolytes in the urine, resulting in dehydration and impaired insulin absorption. Under these conditions, diabetes control is more difficult and ketoacidosis may ensue.

Insulin-dependent diabetes mellitus in children, particularly when poorly controlled, is associated with changes in growth dynamics.[12,13] Since the short stature of 48% of our patients with IDDM and acid peptic disease was not familial, it is tempting to speculate that gastrointestinal problems may result in a poor nutritional status and hence reduced growth rates.[14] Although the height percentile of a statistically significant proportion of the patients with IDDM and acid peptic disease was low, it must also be noted that their HbA_{1c} levels could not be distinguished statistically from those of matched control patients with IDDM, possibly because the HbA_{1c} level is not a sensitive enough indicator of mild but significant hyperglycemia. In addition, it was our clinical observation in some patients that a decrease in height velocity preceded the diagnosis of acid peptic disease and an acceleration then often followed successful therapy. That the reduced height of the patients with IDDM and acid peptic disease did not result from untimely sexual development was confirmed by the fact that their Tanner pubertal stages were not different from corresponding IDDM controls.

Improved diagnostic techniques for acid peptic disease have not eliminated the need for clinical suspicion of any gastrointestinal symptoms, which is especially critical for early diagnosis. Despite our vigilance for this complicating problem, two patients with the most severe cases presented with only mild symptoms, and final diagnosis was delayed. It appears that many patients who experience gastrointestinal symptoms are not evaluated and examined by endoscopy until diabetes control, compliance to treatment regimens, and/or growth expectations are compromised. We recommend routine endoscopic examination of patients with IDDM who are experiencing difficulty with either diabetes control or poor growth in the presence of abdominal pain, nausea, and early satiety.

The frequency of episodic recurrence of acid peptic disease in our patients is comparable with that seen in previous reports of peptic ulceration in nondiabetic patients.[4] Acid peptic disease is typically chronic, requiring continued monitoring and long-term drug therapy. The substantial reduction in the number of hospitalizations after successful treatment of acid peptic disease has major economic and social implications. Early diagnosis and successful treatment of acid peptic disease in patients with IDDM should contribute to ease of diabetes control as well as reduce or delay the onset of IDDM-related complications associated with poor control and poor nutritional status.

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INDICATIONS: For reduction of fever in patients aged 6 months and older, and relief of mild-to-moderate pain in patients 12 years and older; for relief of the signs/symptoms of juvenile arthritis, rheumatoid arthritis and osteoarthritis; for relief of primary dysmenorrhea.

CONTRAINDICATIONS: Hypersensitivity to ibuprofen. Do not give to patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risks of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In clinical trials occurrence of serious GI toxicity is about 1% after 3-6 months of therapy; 2%-4% after one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no factors have been associated with increased risk. Elderly or debilitated patients tolerate ulceration or bleeding less well and have more fatal GI events.

PRECAUTIONS: General: Serious GI tract ulceration and bleeding can occur without warning symptoms; follow chronically treated patients for signs/symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints discontinue the drug and have an ophthalmologic examination performed.

Fluid retention and edema have been reported, therefore, use with caution in patients with history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation, although less than aspirin does, and prolong bleeding time (but within the normal range). Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Liver Effects: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Evaluate patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of more severe hepatic reactions while on ibuprofen therapy. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, discontinue ibuprofen.

Hemoglobin Levels: Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding it is probably not clinically important.

In two ibuprofen postmarketing studies a decrease in hemoglobin of 1 gm or more was observed.

Aseptic Meningitis: While rare, aseptic meningitis with fever and coma has occurred in patients on ibuprofen. Although more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adults without an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, consider the possibility of its being related to ibuprofen.

Renal Effects: Like other NSAIDs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome have been reported. A second form of renal toxicity is seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, NSAIDs may cause a dose-dependent reduction in prostaglandin formation and precipitate overt renal failure; patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly are at greatest risk. Monitor renal function in patients at high risk who take ibuprofen chronically if they have signs or symptoms of azotemia. Discontinuation of NSAIDs is typically followed by recovery. Since ibuprofen is eliminated primarily by the kidneys, closely monitor patients with significant renal impairment and anticipate a dosage reduction to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss potential risks (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**) and likely benefits with patients.

Drug Interactions: *Coumarin-type Anticoagulants:* Short-term studies did not show a significant effect of ibuprofen on a variety of clotting factors when given with coumarin-type anticoagulants. However, bleeding has been reported when ibuprofen or other NSAIDs were administered to patients on these medications; use caution when administering ibuprofen to such patients.

Aspirin: In animal studies, concomitant aspirin/NSAID therapy yielded a net decrease in anti-inflammatory activity with lowered NSAID blood levels. Single dose bioavailability studies in normal volunteers failed to show an effect of aspirin on ibuprofen levels.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Use caution if ibuprofen is administered concomitantly.

H_2 Antagonists: In human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant ibuprofen therapy, observe the patient closely for signs of renal failure and to assure diuretic efficacy.

Lithium: Ibuprofen elevated plasma lithium levels (15%) and reduced renal lithium clearance (19%) in normal volunteers. Observe patients carefully for lithium toxicity. Read lithium package insert before its use.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose; consider this when treating patients with impaired glucose tolerance. It also contains sorbitol, 350 mg/5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than controls, if diarrhea develops, the physician may wish to review other sources of sorbitol in the patient's diet.

Pregnancy/Nursing Mothers: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy in children < 6 months old have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction is gastrointestinal (GI). In adult clinical trials involving chronic ibuprofen administration, 4%-16% of patients reported one or more GI complaints.

Incidence Greater Than 1% (but < 3%) During Controlled Clinical Trials In Adults, Probable Causal Relationship: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence); dizziness,* headache, nervousness; rash* (including maculopapular type), pruritus; tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation, see **PRECAUTIONS**).

Precise Incidence Unkown (but < 1%), Probable Causal Relationship (see **PRECAUTIONS**): Gastric or duodenal ulcer with bleeding and/or perforation, GI hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests, pancreatitis; depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision); neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coomb's positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasm (see **CONTRAINDICATIONS**); acute renal failure, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unkown (but < 1%), Causal Relationship Unknown: Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; toxic epidermal necrolysis, photoallergic skin reactions; conjunctivitis, diplopia, optic neuritis, cataracts; bleeding episodes (eg., epistaxis, menorrhagia); gynecomastia, hypoglycemic reactions, acidosis; arrhythmias (sinus tachycardia, sinus bradycardia); serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema; renal papillary necrosis.

**Reactions occurring in 3%-9% of adult patients treated with ibuprofen. Reactions occurring in < 3% are unmarked.*

OVERDOSAGE: Induce emesis or perform gastric lavage. Oral activated charcoal may be useful in addition to supportive therapy. Because the drug is acidic and excreted in the urine, administration of alkali and induction of diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg total daily dose. Fever: Children 6 months to 12 years of age—5 mg/kg if baseline temperature is 102.5 °F or below, or 10 mg/kg if baseline temperature is greater than 102.5 °F, every 6-8 hours; Adults—400 mg every 4-6 hours. Mild to moderate pain in adults: 400 mg every 4 to 6 hours prn. Juvenile Arthritis: 30-40 mg/kg/day in 3 or 4 divided doses.
RA and OA: 1200-3200 mg daily in 3 or 4 divided doses (adults).
Dysmenorrhea: 400 mg every 4 hours prn.

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Cerebral Palsy and the 'Bad Baby' Malpractice Crisis

New York State Shines Light Toward the End of the Tunnel

Headlines proclaim, "Brain Damaged Child Awarded $10 Million"! "Obstetricians Flee Practice." "Pregnant Women Cannot Find Doctors." You have seen them too frequently. They are signs of the all-too-familiar malpractice insurance crisis. In light of some new proposed solutions, it is worth reviewing the causes of this crisis and approaches to a solution.

There are a variety of factors driving the obstetric malpractice crisis and each has several causes. One factor is our increasingly litigious society that seeks compensation for an injury whether or not that injury was another person's fault. The publicity surrounding the occasional huge multimillion-dollar verdicts and the increasing size of settlements and awards in malpractice cases in general have made the tort system a growth industry for lawyers and have made lawsuits an appealing solution for parents who see an otherwise bleak and expensive future for their impaired child. A second factor is pure misinformation. Because cerebral palsy (CP) is a result of damage to the brain and because a lack of oxygen at birth *can* cause brain damage, many physicians still wrongly believe that perinatal asphyxia is a common cause of CP. The pediatrician becomes a factor in lawsuits when he or she notes an infant's low Apgar scores and, often unthinkingly, writes in the chart "perinatal asphyxia." This diagnosis is carried throughout the child's subsequent medical history. If that child later is found to have CP, it is assumed to be the result of the previously documented perinatal asphyxia. When the parents of that child want to know the cause of their child's disability, perinatal asphyxia becomes a convenient scapegoat and, "we don't know" is often an unacceptable answer.

Obstetricians also have contributed to the crisis. They have convinced themselves, and the public, that healthy newborns are the result of their good obstetrical care. However, a corollary of that thinking is that a less than healthy newborn must be the obstetrician's fault. Obstetricians have developed technology such as fetal monitoring that "reassures" them that the fetus is fine. They then respond to a fetal monitoring strip that is less than reassuring by performing a cesarean section. If they do not intervene, and if that infant later has CP, then their colleagues freely state, "I would have done a cesarean section earlier and the infant would not have suffered brain damage." How do they know that the fetus wasn't already abnormal and that the less than reassuring monitoring strip was the result of or the manifestation of that prior abnormality? How do they know that earlier intervention would have altered the outcome?

A further cause of the malpractice insurance crisis is the use of so-called expert witnesses. Expert witnesses in these cases may or may not have documented expertise in the relationship of perinatal hypoxic-ischemic injury to brain damage. The witnesses' expertise is rarely documented in the literature where it could be subjected to peer review. The courts permit these alleged experts to offer opinions that may be idiosyncratic and far from the mainstream. Some of these experts work exclusively as advocates for the plaintiff or for the defense rather than as experts for the courts, which would be more proper.

For the benefit of those who would be experts, what are the facts—just the facts—about the relationship between hypoxia and/or ischemia and CP?

1. Cerebral palsy *can* be caused by hypoxia or ischemia but it rarely is. Only 4% of the cases of CP are due to asphyxia[1] and another 4% may be related to it, but at least 92% of the cases of CP are not caused by asphyxia. We do not know the cause of most cases of CP. Most cases of CP are likely caused by a variety of prenatal developmental insults. Even when CP is secondary to hypoxic-ischemic brain injury, that injury may not have been preventable.[2] Low Apgar scores alone are not evidence of sufficient perinatal asphyxia to cause brain damage. Low Apgar scores are evidence of a depressed newborn who may need resuscitation. This depression can have many causes, hypoxia being only one. To cause brain damage, hypoxia must be severe and/or prolonged. Apgar scores of less than 3 at 1 minute after birth have no correlation with subsequent outcome. Scores of less than 3 at 5 minutes after birth have little correlation with outcome.[3] Low Apgar scores at 5 minutes after birth, *and* evidence of hypoxic-ischemic encephalopathy, *and* seizures that start within the first 48 hours after birth are good evidence of severe encephalopathy that *can* be the result of prolonged intrauterine

hypoxia. This constellation of findings is highly correlated with the infant's death or subsequent CP.[4] However, 25% of children with even these findings *do not* have subsequent CP. Severe hypoxia usually will affect other organs in addition to the brain. Other prenatal or perinatal conditions may mimic the signs and symptoms of perinatal hypoxia.

2. The fetal monitoring strip that once was believed to provide reassurance to the obstetrician about fetal well-being turns out to be no more reliable than listening to the fetal heart rate.[5] While evidence of decelerations of different types are subject to different interpretations, only prolonged late decelerations and prolonged bradycardia of less than 60 beats per minute are considered to be signs of severe fetal distress, and even these signs have not been correlated with later CP.[6]

3. Acidosis of the newborn's umbilical cord blood should be evidence of intrauterine asphyxia, but even umbilical cord blood with a pH of 7.0 has no correlation with later CP. Perhaps an even lower pH will show correlation with adverse outcome, but it occurs so infrequently that studies cannot be performed.[7]

One could go on refuting the misconceptions about perinatal asphyxia, but this will neither solve the malpractice insurance crisis nor correct problems of the liability tort system.[8] In a rational world, the trial in an alleged perinatal asphyxia case would be bifurcated into causation and malpractice. The court would first ask the question, "Is the child's CP due to asphyxia?" The court then would seek sufficient evidence of the effects of hypoxia and/or ischemia to establish that the child might have been damaged as a result.[9] It also would seek evidence of alternative causes for the child's neonatal symptoms and/or current motor deficit. Only then, once the child's CP was found, with a reasonable degree of medical certainty, to be due to hypoxic and/or ischemic injury, would the court seek to establish the presence or absence of fault and, thereby, liability. Only then would the court ask, "Could that injury have been prevented?" For example, abruptio placenta certainly can cause severe asphyxia to the fetus and can result in brain damage. However, if the abruption were to occur at home, then the damage would not have been preventable by the obstetrician. Therefore, the child's CP could not be the result of obstetric negligence. In this country, causation cannot be tried separately from fault and the two become intertwined.

While we would like to reform the current tort system, change the standards of and for expert witnesses, and improve the evidence submitted to the jury,[8] if we are to use our current legal system as the mechanism for compensating individuals for injuries then the courts first must attribute fault. Currently, in an attempt to compensate these handicapped children, juries may find fault even where it does not exist. The current system is inefficient, expensive, compensates only a small minority of the children with CP, and has huge transaction costs. There is no evidence that the current system either prevents malpractice or punishes physicians who commit malpractice.[10]

But the legal system is not the only approach to compensation of handicapped children and their families. There is a better way, a more just and equitable system that will compensate all children with CP for their medical and rehabilitation costs at considerably less expense than the current tort system. That approach, a true no-fault system, is almost here, at least in New York State.

In 1991, New York State Assembly Bill 8793[10] was introduced at Gov Mario Cuomo's request. The legislation is intended "to create a system to compensate newborns who suffer a medical impairment at birth, without need to prove physician fault." While not the only proposed no-fault legislation (there are no-fault laws in existence in Florida and Virginia and proposed legislation pending in North Carolina[11]), the New York proposal would be the broadest and most comprehensive. If passed, it would assure that all children with CP would receive the same level of medical and rehabilitation services without having to prove fault to attain them. These payments would cover needs over and above those provided by insurance and other state and federal programs. The legislation prohibits the right to sue for damages and thus eliminates the need to find fault.

To quote from the statement of support for this legislation, ". . . the [tort] system ultimately disserves the legitimate interests of impaired newborns, health care professionals and society in general. . . . While most impaired newborns obtain no recovery under the tort system, many . . . receive large monetary awards making the system akin to a 'lottery.' . . . [There is a] tenuous relationship between awards and fault."

In a recent analysis of the Maryland obstetrical malpractice experience,[12] we also called attention to this lottery factor. We found that fewer than 10% of children with CP recovered anything from the tort system in Maryland, yet payments made to those children accounted for more than half of the money insurance companies paid for obstetrical malpractice. Over half of that money went not to the children or to their families but to the lawyers and expert witnesses as transaction costs. In 1989, we proposed no-fault legislation[13] similar to that recently introduced in New York by Governor Cuomo, but it was to be paid for by an assessment on each delivery. We estimated that such a worker's compensation-type system could, by eliminating the transaction costs, pay all of the handicap-related expenses of all children with CP at about half the cost of current obstetrical malpractice premiums.[12]

Cerebral palsy is an expensive tragedy for both the child and the family and can never be adequately recompensed. Ninety percent of the time it is no one's fault. The least a caring society can do is to relieve these families of excess medical costs while providing adequate care to allow these children to achieve their potential. For most children with CP, the current tort system does not achieve these goals. Furthermore, it rarely punishes physicians who do cause injury, and it does not decrease the chance of injury. It is about time that society found a better way to achieve all of these goals. The bill introduced by Governor Cuomo does that. Its no-fault compensation elements provide optimal care for the children. To discipline the small number of physicians who practice poor obstetric care, each case presented for compensation will be reviewed for evidence of poor physician or hospital performance. In addition, the bill contains new requirements for the periodic recredentialing of physicians.

At last, there is a glimmer of light at the end of the malpractice insurance crisis tunnel. The pediatric community should keep abreast of these emerging elements in the legislative field. We should support these efforts to help our patients with CP and their families and work to end the inequities of the "bad baby lottery."

The legal fraternity will complain that families are being deprived of their "right" to sue. True, but in return all children with CP will be given the care they need. Granted, the children will not be compensated for pain and suffering, but it is not clear that pain and suffering can ever be compensated. The lawyers will claim that "bad doctors are not being punished," but the New York bill provides a mechanism for reviewing the quality of care, reeducating physicians who need reeducation, and removing the credentials of others who deserve that form of discipline. It is our opinion that the trial lawyers' actual but unstated complaint concerns their loss of income. The New York bill will distribute the money that previously went to lawyers' and witness' fees among the needy children who have CP.

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Mario A. Luna, MD; Sang Sook Lee, MD; Helmuth Goepfert, MD
(*Arch Otolaryngol Head Neck Surg.* 1992;118:472-476)

Usefulness of Computed Tomographic Scan in the Evaluation of Sensorineural Hearing Loss in Children

Douglas Shusterman; Steven D. Handler, MD; Roger R. Marsh, PhD;
Larissa Bilanuik, MD; Lawrence W. C. Tom, MD
(*Arch Otolaryngol Head Neck Surg.* 1992;118:501-503)

Follow-up of Endoscopic Sinus Surgery on Children With Cystic Fibrosis

James Paul Cuyler, FRCSC
(*Arch Otolaryngol Head Neck Surg.* 1992;118:505-506)

The Impact of Health Care Financing on Childhood Immunization Practices

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• *Objective.*—To examine the impact of patient insurance status and third-party payment methods on physician immunization practices.

***Design.*—Family practice physicians and pediatricians were surveyed to determine whether differences existed in office immunization practices for five childhood vaccines across insurance and payment classes.**

***Setting.*—Milwaukee, Wis.**

***Participants.*—Of 202 Milwaukee area physicians who administer immunizations routinely, 161 (79.7%) returned the questionnaire.**

***Results.*—Physicians reported immunizing uninsured patients in their offices less often than patients with insurance. When insurance does not pay for immunizations, most physicians (81.6%) said that they left the decision of whether to pay for private immunizations or seek free immunizations from the city health department to the family. Physicians estimated that approximately half of their uninsured patients decline private immunizations. Some physicians (20%) who treat patients receiving Medicaid reported that they immunize patients with Title 19 coverage less often than patients with other types of insurance. No significant differences in frequency of immunization were reported for patients insured by capitated-payment health maintenance organizations, fee-for-service health maintenance organizations, or traditional insurance covering immunizations.**

***Conclusions.*—Physicians reported that they do not immunize uninsured and underinsured children as frequently as insured children. Further research is recommended to evaluate the impact of Medicaid enrollment on access to immunization and to develop innovative financing arrangements to ensure that no children leave their physicians' offices without being immunized.**

(*AJDC.* 1992;146:728-732)

One of the great accomplishments of 20th century medicine is the development of safe, effective, low-cost vaccines against many of the most serious illnesses of childhood. Moreover, the recent invention of recombinant gene technology ensures more and better vaccines for the future. In theory, many diseases could be completely eliminated. This is especially true in wealthy countries like the United States that have both the scientific and industrial capacity to produce the necessary vaccines and the health care infrastructure to administer them.

Therefore, it is notable that the United States has not succeeded in fully immunizing our at-risk population. Despite the guidelines on immunizations widely disseminated by the American Academy of Pediatrics and the Immunization Practice Advisory Committee of the US Public Health Service, only 77% of all 2-year-old children were fully immunized in 1985 (Centers for Disease Control, unpublished data, 1987). No national data are available beyond 1985 because federal funding to the Centers for Disease Control for vaccine status surveillance was discontinued in that year. However, surveys of specific high-risk areas have revealed immunization rates as low as 49%.[1]

The incidence of vaccine-preventable childhood diseases, such as mumps, rubella, pertussis, and measles, have increased in recent years.[2-4] The incidence of measles during the first 20 weeks of 1990, for example, was 40% greater than during the equivalent period in 1989, the year in which the highest number of cases in the entire decade was recorded.[5]

These trends suggest the need for a wide-ranging evaluation of physicians' immunization practices and public health policy to identify and eliminate the causes of inadequate immunization. To improve our understanding of the reasons for inadequate immunization, we surveyed primary care physicians in Milwaukee, Wis, a midsized, urban center where a measles epidemic (1107 cases reported) occurred between 1989 and 1990 among predominantly unvaccinated children.[6] The objective of the study was to identify possible financial barriers to immunization by asking physicians about the impact of financial considerations, including insurance status and third-party payment methods, on their immunization practices.

METHODS

In January 1990, a questionnaire was mailed to family practice physicians and pediatricians practicing in the metropolitan Milwaukee area during the measle epidemic. The questionnaire asked physicians about their immunization practices, their

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financial arrangements with third-party payers, and their reasons for not vaccinating patients. The survey covered five childhood immunizations: diphtheria and tetanus toxoids and pertussis vaccine; trivalent oral polio vaccine; *Haemophilus* b conjugate vaccine; and first and second doses of measles-mumps-rubella vaccine (MMR).

To compare responses across insurance and third-party payment classes, we questioned physicians about their immunization practices for uninsured patients and for patients with various types of insurance (traditional insurance, health maintenance organization [HMO], and Title 19). Health maintenance organizations were classified as belonging to one of three types: those employing physicians (salaried staff HMOs); those paying physicians for services performed (fee-for-service HMOs); and those paying physicians a flat amount per patient regardless of services rendered (capitated-payment HMOs).

The questionnaire was modified based on results of pretests, interviews with practicing pediatricians, and a small pilot mailing. The questionnaire was mailed by the City of Milwaukee Department of Health to all pediatricians, family practice specialists, and general practitioners who were treating children in the metropolitan Milwaukee area during the 1989-1990 measles epidemic.

The population of children's physicians was identified from a listing of physicians with practicing privileges at Children's Hospital of Wisconsin, the primary inpatient pediatric facility serving the area. To verify its completeness, the list was cross-checked against the Milwaukee County Medical Society's list of pediatricians. After eliminating subspecialists and physicians who were not practicing at the time of the study, the survey was mailed to 202 physicians in the Milwaukee area who routinely administer childhood immunizations.

A follow-up letter and second questionnaire were sent to nonrespondents. Of the physicians contacted, 161 (79.7%) returned the questionnaire. The responses were analyzed using nonparametric techniques[7] to determine whether differences were reported in physicians' immunization practices across vaccine and insurance types.

RESULTS

To examine the effect of insurance coverage on immunization practices, we asked physicians how often they administered each of the five vaccines (diphtheria and tetanus toxoids and pertussis vaccine, trivalent oral polio vaccine, *Haemophilus* b conjugate vaccine, and first and second doses of MMR) when the child's insurance pays for immunization vs when it does not. Comparisons of physicians' responses across insurance types revealed significant differences.

Table 1 presents the distribution of responses for two of the five vaccines. Physicians reported administering both trivalent oral polio vaccine and MMR (second dose) less often when insurance does not pay for immunizations. Similar results were found for diphtheria and tetanus toxoids and pertussis vaccine, *Haemophilus* b conjugate vaccine, and MMR (first dose). Responses of physicians who treat both insured and uninsured children were compared using Wilcoxon signed rank tests for matched pairs. Test results showed that physicians reported administering all five types of vaccines to uninsured patients less often than to insured patients ($P<.01$). No significant differences were found in the frequency of administering any one of the five vaccines in a given insurance type.

When insurance does not pay for immunization, most physicians (81.6%) said that they leave to the family the decision of whether to pay for private immunization or take the child to the public health department for free immunization. Less than 10% reported that they routinely immunized children when insurance did not pay. Only 8.8% said that they routinely refer uninsured children to the public health department rather than leaving the decision to the parents. When the choice was left to the family, physicians estimated that approximately half (50.7%) of the uninsured families choose to have their children immunized at the health department rather than paying for private immunizations.

Table 1.—How Often Physicians Administer Specific Vaccines When Insurance Pays for the Vaccines vs When It Does Not*

Frequency of Vaccination	Pays OPV	Pays MMR, 2nd Dose	Does Not Pay OPV	Does Not Pay MMR, 2nd Dose
Always	114 (74.0)	111 (74.0)	33 (28.0)	30 (26.3)
Almost always	34 (22.1)	32 (21.3)	30 (25.4)	28 (24.6)
Frequently	4 (2.6)	4 (2.7)	32 (27.1)	34 (29.8)
Occasionally	1 (0.6)	2 (1.3)	23 (19.5)	20 (17.5)
Never	1 (0.6)	1 (0.7)	0	2 (1.8)
Total	**154 (99.9)**	**150 (100)**	**118 (100)**	**114 (100)**
No response, No. of cases	7	11	18	22
Not applicable, No. of cases†	0	0	25	25
Total	**161**	**161**	**161**	**161**

*Values are number (percentage) of responses except where indicated. OPV indicates oral polio vaccine, and MMR, measles-mumps-rubella vaccine. Percentages may not total 100 because of rounding.

†Respondents had no uninsured patients.

To examine the effect of insurance type and third-party payment method on physician immunization practices, we asked physicians how often they immunized patients in five different pay classes: (1) patients who pay out-of-pocket (those who are uninsured or whose insurance does not cover immunizations); (2) patients belonging to capitated-payment HMOs; (3) patients belonging to fee-for-service HMOs; (4) patients with traditional insurance covering immunization; (5) and patients covered by Title 19 (Medicaid). Physicians' responses are summarized in Table 2.

The results of this portion of the questionnaire confirmed the previous finding: physicians reported immunizing uninsured children less often than insured children, irrespective of the payment method or type of insurance coverage of the insured patients. Paired comparisons of the responses showed that physicians who treat both insured and uninsured children immunize patients who pay out-of-pocket for immunizations less often than patients with any of the four types of insurance (capitated-payment HMOs, fee-for-service HMOs, traditional insurance, and Title 19).

Physicians reported no differences in the frequency of immunizing patients insured by HMOs or traditional insurance plans that cover immunizations. No significant differences were found in physician immunization practices between patients in capitated-payment HMOs and patients in fee-for-service HMOs or between patients with traditional insurance and patients in either type of HMO.

Table 3 presents results of paired comparisons of frequency of vaccination based on responses by physi-

Table 2.—Frequency of Vaccination According to Type of Patient Health Insurance*

Frequency of Vaccination	Uninsured†	Capitated-Payment HMO	Fee-for-Service HMO	Traditional Insurance	Title 19 Coverage
Always	21 (17.1)	42 (72.4)	59 (62.8)	85 (67.5)	77 (59.7)
Almost always	19 (15.4)	11 (19.0)	31 (33.0)	34 (27.0)	37 (28.7)
Frequently	47 (38.2)	4 (6.9)	2 (2.1)	4 (3.2)	7 (5.4)
Occasionally	33 (26.8)	1 (1.7)	2 (2.1)	2 (1.6)	6 (4.7)
Never	3 (2.4)	0	0	1 (0.8)	2 (1.6)
Total	**123 (99.9)**	**58 (100)**	**94 (100)**	**126 (100.1)**	**129 (100.1)**
No response, No. of cases	13	13	12	12	14
Not applicable, No. of cases‡	25	90	55	23	18
Total	**161**	**161**	**161**	**161**	**161**

*Values are number (percentage) of responses except where indicated. HMO indicates health maintenance organization. Percentages may not total 100 because of rounding.

†Uninsured patients were defined as those without insurance or whose insurance did not include immunization.

‡Respondents had no patients in this pay class.

Table 3.—Matched-Pair Comparisons of Frequency of Vaccination Based on Responses of Physicians Who Treat Both Patients With Title 19 Coverage and Patients With Other Types of Insurance*

Title 19 Coverage vs Other Insurance	Pairs†	Ties‡	Patients With Title 19 Coverage Vaccinated Less Often	Patients With Title 19 Coverage Vaccinated More Often	*P*
Capitated-payment HMO	58	44	11	3	.05
Fee-for-service HMO	90	65	19	6	.01
Traditional insurance	119	87	23	9	.02
Total, No. (%) of Responses	**267** (100)	**196** (73)	**53** (20)	**18** (7)	NA

*Except for the last row and last column, values are number of responses in each category. HMO indicates health maintenance organization, and NA, not applicable.

†Number of respondents who treat both patients with Title 19 coverage and patients with the other indicated type of insurance.

‡Number of respondents who reported no difference in the frequency of vaccinating patients with Title 19 coverage vs patients with the other indicated type of insurance.

cians who treat both patients with Title 19 coverage and patients with other types of insurance as indicated by the large percentage of ties (73%), in most cases physicians reported no differences in the frequency of immunizing patients with Title 19 coverage vs patients with any of the three other types of insurance.

In a minority of cases (20%), physicians said that they immunized patients with Title 19 coverage less often than patients with other types of insurance. The reported difference in the frequency of immunizing children with Title 19 coverage was statistically significant. Wilcoxon signed rank tests for matched pairs were used to test the null hypothesis that there is no difference between the reported frequency of immunization of patients with Title 19 coverage and patients with any of the three other types of insurance. In all three cases, the null hypothesis was rejected ($P = .01$, $P = .02$, and $P = .05$). Results of similar tests indicated no significant differences in physician immunization practices among patients insured by HMOs or traditional insurance.

Although most physicians (71%) said that they never decline to immunize because of inadequate reimbursement, they are not uniformly satisfied with third-party payment arrangements. Results of the survey revealed a wide difference in physician satisfaction with immunization payment arrangements across HMO types. Table 4 presents physicians' perceptions of the adequacy of HMO payments by HMO type. Physicians who contract with capitated-payment HMOs are the least satisfied: most physicians who contract with capitated-payment HMOs reported that less than 50% of the HMOs accepted by their practices pay adequately for immunizations. Physicians reported higher levels of satisfaction with salaried-staff and fee-for-service HMOs.

Physicians cited medical judgment and parental choice as the most important factors influencing their decisions not to immunize patients. When asked to rate the importance of several reasons for not immunizing, physicians rated the adequacy and speed of third-party payments and the cost of vaccines as relatively unimportant factors. Among the financial reasons for not immunizing patients, physicians cited the lack of insurance coverage as most important.

COMMENT

The questionnaire results indicated that lack of insurance is a barrier to immunization in private practices. Physicians reported a significant difference in the frequency of immunization of insured vs uninsured children, citing the choice of uninsured parents as a major reason for immunization referrals to public health services. Because the study relied on self-reports and physicians' recall of immunization practice patterns, responses may have been subject to estimation and reporting bias. However, our results are consistent with those of a recent study of immunization referral patterns in Dallas County, Texas. Dallas physicians surveyed by Schulte et al[8] reported a 693% increase in the number of children

Table 4.—Percentage of HMOs Accepted at Responding Physicians' Practices That Adequately Reimburse for Vaccinations*

	Type of HMO Contract				
% of HMOs Reimbursing Adequately	Salaried Staff	Capitated Payments	Fee-for-Service Payments	Capitated Payments and Fee-for-Service Payments	Total
<50	5 (23.8)	7 (77.8)	17 (37.0)	10 (62.5)	39 (42.4)
≥50	16 (76.2)	2 (22.2)	29 (63.0)	6 (37.5)	53 (57.6)
Total	**21 (100)**	**9 (100)**	**46 (100)**	**16 (100)**	**92 (100)**

*Values are number (percentage) of responses for each type of health maintenance organization (HMO). $\chi^2=10.8$ and $df=3$.

referred to public health clinics between 1979 and 1988 and cited the inability of patients to afford private immunizations as the primary reason for the referrals.

Because coverage provided by state Medicaid programs differs substantially, the findings concerning Title 19 and capitated-payment HMOs cannot be generalized. Wisconsin's Medicaid program is unique in that only 8% of Milwaukee's Medicaid recipients are enrolled in a fee-for-service program, which is typical of Title 19 programs in other states, while 92% are enrolled in commercial HMOs through a capitated-payment arrangement between the state and local HMOs. Because participating HMOs are contractually obligated to provide well-baby care, including immunizations, to Medicaid recipients, the incidence of Medicaid referrals to public facilities should be lower in Milwaukee than in other cities with standard Title 19 programs.

Although the questionnaire results suggested that HMO payment arrangements do not influence physician immunization decisions, differences in physicians' perceptions of the adequacy of HMO payments methods may influence the extent to which physicians implement proactive immunization programs. The Milwaukee measles epidemic indicates a potential gap between the disease prevention/health maintenance philosophy of HMOs and actual practice. Of the 20 000 children immunized free of charge by the city health department during the epidemic, 55% were HMO members. Only one of Milwaukee's six major HMOs (a salaried staff HMO) expended significant new resources to aggressively immunize high-risk clients during the epidemic (*The Milwaukee Sentinel.* July 17, 1990:1).

Prior research[9] indicated that Medicaid pays physicians considerably less than do other payers for office procedures and suggested that lower payments may limit access to private care for Medicaid recipients. Our finding that some physicians reported immunizing patients with Title 19 coverage less often than patients with other types of insurance may, however, be due to factors unrelated to financial considerations, such as the unavailability of immunization records or higher incidence of illness. Further research is needed to assess the impact of Medicaid payment levels on access to childhood immunization in the private sector. Among research issues that should be addressed is whether physician behavior is influenced by the proportion of Medicaid recipients in their practices, possible disparities between the actual and perceived adequacy of Medicaid payments, and interstate variations in Medicaid payment arrangements.

POLICY IMPLICATION

From a health policy perspective, the questionnaire results indicated the need to eliminate financial barriers to private-sector immunization of uninsured and underinsured children. The fact that immunizations are provided free of charge by public health departments to uninsured children has not proved sufficient to guarantee that all children will be immunized regardless of financial means. Milwaukee Health Department records indicate that the measles vaccination rate for 2-year-old children was only 60% before the 1989-90 epidemic. The measles vaccination rate in Chicago, Ill, was only 49% before its recent epidemic.[1] An aggressive, proactive campaign to immunize all at-risk children will require participation by both the public and private sectors and financial arrangements that allow and encourage private physicians to immunize all their patients regardless of insurance coverage.

Our results indicated that physicians do not immunize uninsured and underinsured patients as frequently as children with insurance that covers immunization. Moreover, research by Schulte et al[8] found evidence of an increasing trend in the number of physician referrals to public clinics for immunization. This disparity in the site of health care delivery is unacceptable for two reasons.

First, when children leave their physicians' offices without receiving immunization, an opportunity to provide an essential preventive care service is lost. There is no assurance that families who decline immunizations in their physicians' offices for financial reasons will subsequently have their children immunized by public health departments or do so in a timely manner. The extent of parental follow-through and physician follow-up on immunization referrals has not been adequately assessed. However, initial evidence suggests that referral results in less complete immunization. In an audit of private-practice physicians' immunization records, McDaniel et al[10] found that children who received their immunizations exclusively from their private physicians were better immunized than those who received immunizations from both their private physicians and health department clinics.

Second, the term *parental choice* is potentially misleading given the composition of the uninsured population in the United States. While families with private insurance that does not cover immunizations are often in higher income brackets and able to pay for private immunizations, uninsured families are less likely to have a choice. Several studies[11-13] report that the uninsured population is composed largely of low income, working individuals and families. Financial restrictions may prevent low income families from having discretionary power in choosing the site at which their children receive health care.

Differential treatment of insured vs uninsured and underinsured children, including children receiving Medicaid, creates a de facto, two-tiered system of preventative health care. Private physicians immunize insured children during the normal course of care, while uninsured families must make special efforts to go outside the primary health care delivery system to receive essential childhood immunizations. At a minimum, a financial system that necessitates referrals of patients from one delivery site to another to take advantage of public financing delays immunization and increases the length of time during which children are at risk of disease. The critical importance of timely immunization was evident in the Milwaukee measles epidemic, which occurred during the time lag between adoption and implementation of the American Academy of Pediatrics recommendation for a second dose of MMR.

Despite a complex array of public and private financing schemes that supposedly ensure access to immunization, insurance status and financial means continue to be barriers to immunization. Consequently, we believe more consideration should to be given to developing innovative financial arrangements that ensure that no child leave his or her physician's office without being immunized.

The State Medical Society of Wisconsin has proposed one such arrangement. In 1990, in response to the Milwaukee measles epidemic, the society adopted a resolution supporting direct, universal federal funding of immunization to allow physicians to aggressively immunize all children regardless of insurance status. In support of a one-payer system, the society noted that, rather than being encouraged to immunize children in their care, physicians face a series of disincentives, such as the high cost of vaccines, the threat of litigation, increased paperwork, irregular or insufficient reimbursement from a bewildering variety of payers, and growing numbers of uninsured and underinsured patients who often decline preventive medical care because of expense.

The cost-benefit, effectiveness, and possible negative consequences of a federal, one-payer system have not been adequately evaluated. Nor have alternative financing options combining federal, state, and private initiatives to increase access to immunizations in private sector settings been sufficiently considered. Nonetheless, an evaluation of a one-payer system for childhood immunizations would be a logical first step to developing a financial system that allows and encourages physicians to immunize all children in their practices regardless of their insurance status.

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The Fasciitis-Morphea Complex in Children

John J. Miller III, MD, PhD

- *Objective.*—To describe the clinical presentation and treatment of the combined syndrome of fasciitis and morphea in children.

Setting.—The rheumatic disease clinic of a university children's hospital.

Patients.—Six children who were referred for signs or symptoms of fasciitis were observed.

Selection Procedures.—All children who were referred for fasciitis were included in the study.

Interventions.—Therapy included prednisone initially and subsequent long-term treatment with penicillamine and alternate-day doses of prednisone.

Measurements and Results.—Symptoms of morphea appeared 1 year before to 4 years after the first signs of fasciitis were observed. The fasciitis was characterized by usually symmetrical, centrifugal swelling, pain, and contracture formation. The morphea and fasciitis did not appear in the same areas of the body.

Conclusions.—The fasciitis and morphea are clearly linked manifestations. The fasciitis, but not the morphea, appears to respond to treatment with steroids. Treatment with penicillamine may ameliorate the sclerosis of the morphea but does not stop new lesions from appearing.

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"Eosinophilic fasciitis" was originally described as an asymmetrical, steroid-responsive form of scleroderma observed in adults. It has also been reported in children, but there has been argument about whether the childhood form is a distinct entity.[1,2] It has been clear that at least some cases progressed to morphea or linear scleroderma.[1-9] One child was reported to have developed systemic sclerosis after an initial presentation with fasciitis,[10] but that is a more difficult differential. The first patient seen at Stanford (Calif) University School of Medicine caused us to raise questions regarding the overlap between eosinophilic fasciitis and morphea.[2] At this time, distinct lesions of morphea or linear scleroderma have developed in all six children seen here with fasciitis. The fasciitis in these children appears to be distinct from the eosinophilic fasciitis that is observed in adults. Moreover, childhood fasciitis and localized scleroderma appear to be different manifestations of the same disease.

The purpose of this article is to describe the common features of the patients seen at Stanford, the delay in appearance of morphea relative to the fasciitis in some of them, and the different responses to therapy of the different lesions in individual patients.

REPORT OF PATIENTS

PATIENT 1.— A 2-year-old girl presented with markedly swollen hands and forearms. Her left leg was also swollen. Her mother had noticed discrete patches of hypopigmentation and hyperpigmentation on her trunk and left arm about 1 year before the swelling started. She had a white blood cell count (WBC) of $21 \times 10^9/L$ with 31% eosinophils, and had hyperglobulinemia. The results of a through-and-through skin-to-muscle biopsy revealed features consistent with eosinophilic fasciitis. The girl was given prednisone starting at 15 mg/d and the swelling and eosinophilia disappeared, but she was left with hyperpigmentation on her trunk and an atrophic left leg. During the succeeding 8 years without further treatment, no new lesions appeared, but the skin of the left leg has the appearance typical of linear scleroderma. The girl has severe functional and cosmetic difficulties because the left leg is 6 cm shorter than the right, and she has restricted ankle movement and a knee contracture.

PATIENT 2.— A 4½-year-old boy presented at Stanford with "arthritis." The parents described his hands and feet as having been abnormal at birth, and physicians who saw him as an infant variously diagnosed arthrogryposis or spastic quadraparesis. He developed a patch of morphea on his back at age 3 years. He first complained of pain in his hands at age 3½. When seen at Stanford, he had an indented and sclerotic lesion of morphea on the lower part of his back (Fig 1). He also had symmetrical, firm, and tender swelling of forearms and calves. Wrist movement was limited and the fingers were contracted due to tightness of the finger flexor and extensor tendons (Fig 2). The toes had similar changes. The knees and elbows had flexion contractures of 10° to 15°. There was no clinical sign of synovitis in any joint. The eosinophils were 9% of an unknown WBC count before referral and 4% of a WBC count of $8.6 \times 10^9/L$ at the time of referral. The erythrocyte sedimentation rate (ESR), creatine kinase levels, aldolase levels, and joint roentgenograms were all normal. A biopsy specimen taken from the thigh revealed inflammation in the deep fascia and adjacent muscle that consisted of predominantly mononuclear cells around blood vessels and thick fibrous trabeculae. The patient was given prednisone (20 mg/d), and in 1 month the swelling was gone. The range of motion of all joints was improved but did not return to normal. The morphea lesion was unchanged. The patient was then given penicillamine (125 mg/d, increased by 125-mg increments to 500 mg/d over a 6-month period) and the prednisone regimen (20 mg) was given every other day. After

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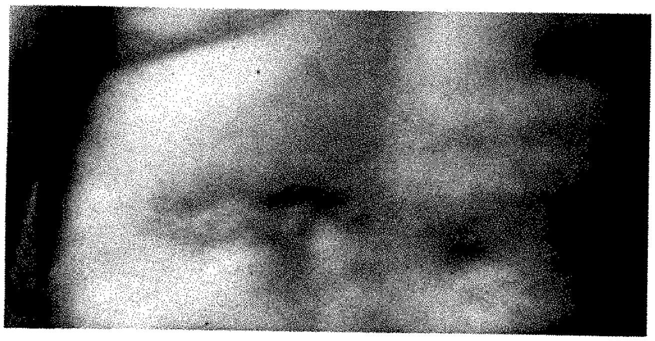

Fig 1.—*Photograph of morphea lesion on the lower part of the back of patient 2. This was an area quite distinct and distant from the areas of fasciitis and muscle contracture.*

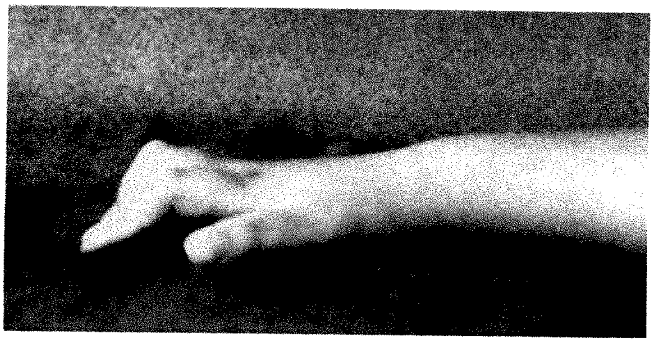

Fig 2.—*The right hand of patient 2, showing the finger contractures resulting from the fasciitis in the forearms. The metacarpophalangeal joints are nearly fixed in a neutral position, but the proximal interphalangeal joints are fixed in flexion. With subsequent growth these joints have become subluxed despite treatment.*

4 years of that regimen, the original morphea lesion persisted as a soft, indented patch. New lesions of morphea have appeared, but have remained superficial with soft, silvery, dermal atrophy surrounded by an irregular hyperpigmented margin.

Patient 3.—A 6½-year-old-girl complained of pain in her neck, arms, and legs. She had symmetrical, tender swelling of her hands and lower legs. The tip of the spleen was palpable, but no other lymphoid hypertrophy was present. She had 11% eosinophils with a WBC count of 7.7×10^9/L, but otherwise her blood cell counts, ESR, antistreptolysin O titer, rheumatoid factor, antinuclear antibody, and *Trichinella spiralis* titers were normal. Roentgenograms revealed normal findings except for soft-tissue swelling. During 5 months without treatment, while tests for allergic and parasitic diseases were pursued in vain, she had progressive loss of the range motion in the wrists, fingers, and ankles. The patient was given a short course of predisone elsewhere and dramatic transient improvement was observed. The results of a biopsy of the forearm, performed 6 months after onset of symptoms, revealed that lymphocytes, plasma cells, and monocytes had infiltrated the muscle, fascia, and deep dermis (Figs 3 and 4). The patient was given a 40-mg/d dosage of prednisone that was tapered over 6 months. The pain and swelling decreased rapidly, the eosinophilia disappeared, and the range of motion in the wrists and feet improved. She continued to require prednisone (20 mg) administered every other day to maintain control of these features. Two years after onset, two small, white patches of skin, suggestive of morphea, appeared on the left knee, and an exaggerated venous pattern appeared over the lower left leg. One year later, a larger, distinct morphea patch appeared on her back. The patient was started on a regimen of penicillamine, gradually increased from 125 to 375 mg/d. Treatment was stopped after 6 months because the lesions appeared to be stable and did not become sclerotic. One year later, treatment was reinstated after new lesions started to appear on her back. In spite of continued treatment, new silvery, nonsclerotic patches continue to appear.

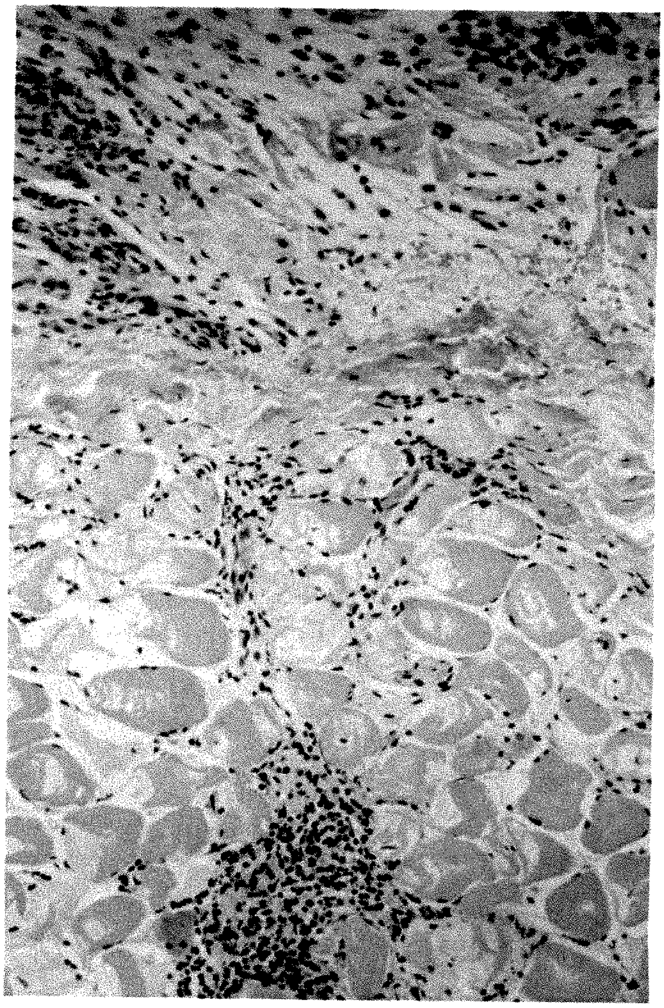

Fig 3.—*The muscle-panniculus interface from patient 3, showing the chronic inflammatory cell infiltrates in the muscle and in the adjacent fascia of the deep panniculus (hematoxylin-eosin, original magnification × 16).*

Patient 4.—A 13-year-old girl first noted pain and swelling of her hands. One year later, the same was noted in the wrists. At age 15, linear scleroderma developed on the back of the left calf. This lesion progressed to the dorsum of the left foot and to the popliteal space. At age 16, when first examined at Stanford, the linear lesion was sclerotic, deeply indented, and it restricted motion in the ankle. The epidermis of the forearms was loose and easily wrinkled, but the underlying fascia and muscles were abnormally firm, and movement of the fingers and wrists was limited and painful. The WBC count was 7.9×10^9/L with 5% eosinophils that later increased to 10%. The ESR was 46 mm/h. The creatine kinase and aldolase levels were normal. She was given penicillamine (250 mg/d) and prednisone (20 mg every other day). The dosage of penicillamine was increased to 500 mg/d after 1 month. After 3 months of therapy, she noted improved range of motion in her hands, the linear lesion had become softer and less indented, and hair started to grow in the lesion. At that point, both medications were stopped. During the succeeding 8 months her condition remained stable with no new lesions or increased tightness.

Patient 5.—A 9½-year-old girl lost the ability to make a fist. In the course of 6 months, tightness of the skin developed on her elbows, shoulders, knees, ankles, and feet. No swelling or redness of any tissues was noted, although an effusion in the knee was seen on one occasion. Her aldolase level was elevated at

11 U/L and the ESR at 19 mm/h, but the results of a complete blood cell count, antinuclear antibody test, anti-ribonucleoprotein antibody test, and roentgenograms were normal. A skin biopsy showed a granulomatous inflammation at the dermal-panniculus border, but a deeper tissue sample was not obtained. She subsequently developed an antinuclear antibody titer of 1/80 with a speckled pattern. She was seen at Stanford at age 10, at which time she had flexion contracture of 30° of her elbows, decreased supination and pronation, and decreased range of motion in the metacarpophalangeal and proximal interphalangeal joints. The knees, ankles, and feet had similar restrictions. There was no clinical evidence of synovitis. The skin of the lower legs was shiny and had a prominent venous pattern. Symmetrical patches of sclerotic, silvery, bound-down skin were present over the medial malleoli and dorsa of the feet. Subsequent to her twin sister's biopsy (see below), she was given penicillamine and prednisone. Six months later, normal function and joint ranges of motion were observed, and therapy was stopped. Recent testing has revealed recurrence of an elevated aldolase level without symptoms, and her physician has reinstituted alternate-day prednisone therapy at a low dose. She was not seen again at Stanford for 3½ years. At that time, she had minimal loss of range of motion in her wrists and ankles, and the morphea lesions that remained were seen only as patches of slightly thinned and hyperpigmented skin.

PATIENT 6.—The identical twin sister of patient 5 experienced a similar loss of range of motion in the hands and feet. On examination at age 10, her symptoms appeared similar to those of her sister, except that her physical restrictions were only half as severe. Her skin lacked the distinct morphea lesions seen in her sister, but shiny skin and prominent veins over the legs were observed. The results of skin, fascia, and muscle biopsy revealed changes consistent with eosinophilic fasciitis. She had normal range of motion in the hands and feet 6 months after she was given penicillamine and prednisone, and medication was stopped. At age 13, a distinct patch of morphea developed in the right popliteal space and extended to the upper posterior calf. Her physician has reinstituted the penicillamine treatment.

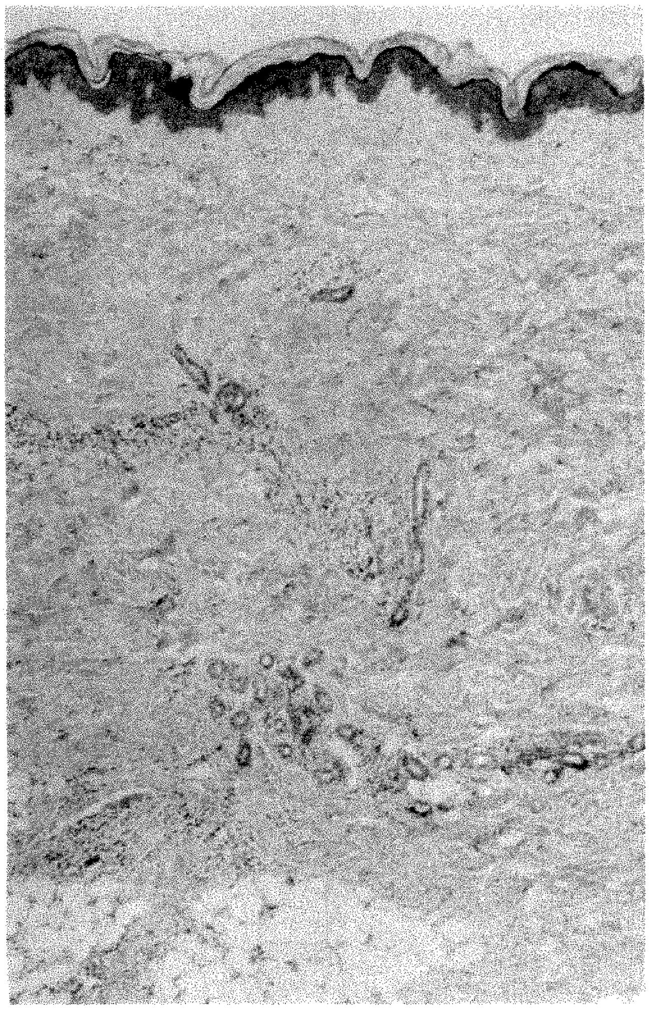

Fig 4.—*The dermis and epidermis of patient 3, showing normal epidermis, fine dermal collagen strands, thickened total dermal layer, and deep trabeculae, with mild inflammation adjacent to sweat glands (hematoxylin-eosin, original magnification ×40). Clinical morphea did not appear until 2 years after this biopsy specimen was taken, and then it appeared on a different part of the body.*

COMMENT

The Table summarizes the most significant clinical and laboratory features of these children. All of the children were affected before the eosinophilic-myalgia syndrome due to tryptophan was recognized, and the parents deny knowledge of any exposure to supplemental tryptophan.

Features of the Six Children With the Fasciitis-Morphea Complex

	Patient No.					
	1	2	3	4	5	6
Race	White	White	White	White	White	White
Sex	F	M	F	F	F	F
Age at onset, fasciitis, y	2	Birth	6½	13	9½	9
Age at onset, morphea, y	1	3	9½	15	9½	13
Highest eosinophil fraction as decimal	0.31	0.09	0.16	0.10	NA	NA
Antinuclear antibody						
Titer	1/640	NA*	1/160	NA	1/80	1/320
Pattern	Diffuse	. . .	Nucleolar	. . .	Speckled	Speckled
Highest erythrocyte sedimentation rate, mm/h	89	9	20	46	19	NA
Highest aldolase level, U/L (normal <7 U/L)	31	7	12	5	11	NA
Result of biopsy	Fasciitis	Fasciitis	Fasciitis	NA	Granulomatous dermis†	Fasciitis

*NA indicates not available or not performed.
†Biopsy not taken deep into fascia.

There is not enough information about the immunoglobulin levels of the patients during the early stages of the disease to know whether they were hyperglobulinemic; therefore, it is not certain whether they had this criterion for eosinophilic fasciitis as defined by Shulman[11] and Rodnan et al.[12] All patients in the study, with the exception of patient 1, had fasciitis in a centrifugal, symmetrical distribution; however, when observed in adults, eosinophilic fasciitis has an asymmetrical distribution.[11,12] None of the children exhibited symptoms of Raynaud's phenomenon or the peau d'orange phenomenon typical of adults.[11,12] However, all of those for whom we have data had eosinophilia at some point. The lesions of morphea appeared on different parts of the body than did the fasciitis, and the morphea was not synchronous with the fasciitis, having appeared from 1 year earlier to 4 years later. It is notable that all six children have had consistently normal creatine kinase levels, but four have had elevated aldolase levels at some time.

These children represent one third of the children with morphea who have been referred to this clinic during the same period of time. It is not possible to conclude that this number is proportionate to the incidence ratio in general because Stanford is a referral center and the children seen here tend to be those with the most severe form of the disease. Nevertheless, the complex of fasciitis with morphea must be relatively frequent. It appears probable that all children seen with fasciitis of this sort are at risk for the development of morphea. This association is not limited to children.[13]

A rapid response to treatment with steroids is part of the definition of eosinophilic fasciitis[11,12] and was shared by these children. Swelling and pain remitted rapidly in all children with those symptoms. Improvement in the flexion contractures also occurred in all patients coincident with the use of steroids but was not necessarily complete and probably varied inversely with the length of time contractures had existed prior to therapy. Administration of steroids alone did not appear to influence the morphea in any way. Coincident with the use of alternate-day steroids and penicillamine, preexisting morphea lesions became less sclerotic, ie, less hard, less deeply attached, and less depressed, but persisted as areas of hyperpigmentation or hypopigmentation. This therapy did not stop new lesions from appearing, but those that did appear consisted of atrophic epidermis, central hypopigmentation, increased venous patterning, and peripheral hyperpigmentation without the expected degree of sclerosis. Morphea usually remits spontaneously, but it can be destructive cosmetically and functionally. Although, to our knowledge, there are no formal studies of the role of penicillamine in the treatment of morphea, current information suggests its use in most cases.

The importance of recognizing the linkage of fasciitis in children with morphea is twofold. First, all children with morphea should be examined for the presence of hand and foot contractures because, if these are due to fasciitis, they may be treated effectively with a relatively short course of steroids. Second, children who present with fasciitis alone must be considered at high risk for developing morphea. This knowledge will lead to early detection and forewarn the patient, the parents, and the physician. Early detection may allow the possibly antisclerotic treatment with penicillamine to start before potentially disabling lesions develop.

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Cerebral Blood Flow Velocity in Normal, Full-Term Newborns Is Not Related to Ductal Closure

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• ***Objective.***—**To correlate changes in blood flow velocity in the anterior and middle cerebral arteries with closure of the ductus arteriosus in normal, full-term newborns during the first 2 days following delivery.**

Design.—**Survey.**

Setting.—**Large community hospital.**

Participants.—**Twenty-three normal, full-term neonates.**

Selection Procedures.—**Volunteer sample.**

Interventions.—**None.**

Measurements and Results.—**We measured blood flow velocity in the anterior and middle cerebral arteries, cardiac output, and patency of the ductus arteriosus using pulsed Doppler, M-mode, and real-time ultrasound. The initial examination was performed at (mean±SD) 7.6±2 hours and the second examination was performed at 30±3 hours. The systolic, diastolic, and mean blood flow velocity in the anterior and middle cerebral arteries increased significantly from day 1 to day 2. Cardiac output did not change significantly (252±49 vs 279±69 cm³/kg per minute). Thirteen newborns on day 1, but only two newborns on day 2, had echocardiographic evidence of a patent ductus arteriosus. Newborns whose ductus was already closed on day 1 had similar increases in blood flow velocity in the anterior and middle cerebral arteries from day 1 to day 2 compared with newborns whose ductus had closed from day 1 to day 2.**

Conclusion.—**The normal increase in blood flow velocity in the anterior and middle cerebral arteries in the first 2 days following delivery is not related to changes in cardiac output or ductal closure.**

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The transition of the cerebral circulation from intrauterine to extrauterine life is complex and incompletely understood.[1-5] It is important to clarify the mechanism of postnatal adaptation of this system because cerebral perfusion abnormalities are involved in the pathogenesis of hemorrhagic and ischemic injuries to the central nervous system in the peripartum period.[1,2,6] Although preterm newborns are at the greatest risk of developing these problems, we need to understand the normal process of postnatal adaptation of the cerebral circulation in full-term newborns.

The development of range-gated, pulsed Doppler ultrasound, coupled with real-time imaging, has made it feasible to investigate noninvasively the cerebral circulation in the newborn by measuring blood flow velocity (BFV) in the anterior cerebral artery (ACA) and middle cerebral artery (MCA).[7-10] This technique can also evaluate the systemic circulation by measuring cardiac output (CO)[7,11-14] and shunting through the patent ductus arteriosus (PDA),[15] two factors that can potentially affect cerebral perfusion. Previous investigators have used pulsed Doppler and real-time imaging of the ACA and MCA to describe a significant increase in BFV in both arteries during the first few days following delivery in normal, full-term newborns.[7,9,10] It is not known whether this increase is secondary to systemic hemodynamic changes or is limited to local central nervous system adjustments. One study suggests that PDA closure may cause the increase in BFV.[7] In this study, 10 newborns (mean age, 4.9 hours) who had a PDA on the first day were evaluated again on the second day when all had a closed ductus. Although the increase in BFV in the ACA and MCA from day 1 to day 2 was temporally related to ductal closure, it may not, in fact, be causally related.

The purpose of this study was to evaluate a larger group of patients to determine whether newborns whose PDA had closed on initial examination on day 1 would still demonstrate an increase in BFV in the ACA and MCA on the second day following delivery.

PATIENTS, MATERIALS, AND METHODS

We studied 23 normal, full-term newborns initially between 4 and 12 hours following delivery, and again 24 hours later. Twenty-one were delivered vaginally and two by cesarean section. All had Apgar scores of greater than seven at 1 and 5 minutes, and none required resuscitation in the delivery room. The results of the physical examinations were all normal. Following informed written consent, we studied the newborns in the supine position in their bassinets within the nursery. Their heads were turned to the contralateral side when studying the ACA and MCA. The newborns were awake, but resting quietly during the entire examination. This sometimes required the use of a pacifier. Cardiac output, ductal shunting, and BFV in the ACA and MCA were evaluated with two-dimensional, range-gated, pulsed Doppler ultrasound (model DRF 400, Orthopedic Equip-

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Table 1.—Cardiac Parameters for 23 Normal Term Newborns

	Mean ± SD			
	Day 1	Day 2	*P**	95% Confidence Interval
Age, h	7.6±2	30±3	. . .	. . .
Heart rate, beats/min	111±15	117±19	.07	−12 to .48
Aortic diameter, cm	.88±.12	.89±.09	.50	−.05 to .02
Stroke volume, cm³/kg per beat	2.32±.52	2.39±.47	.59	−.35 to .20
Cardiac output, cm³/kg per minute				
All patients	252±49	279±69	.10	−5 to 61
Patent ductus arteriosus (n=13)	245±38	. . .	. . .	. . .
No patent ductus arteriosus (n=10)	261±61†	. . .	. . .	. . .

*Two-tailed paired *t* test.

†*P*=.45 vs patent ductus arteriosus by two-tailed, unpaired *t* test; confidence interval, −59 to 27.

ment Co/Diasonics, Milpitas, Calif) using a 7.5-MHz imaging transducer and a 6.0-MHz Doppler frequency with fast-Fourier transform analysis of the Doppler signals. All studies were performed by the same individual (S.R.) and were recorded on videotape to be analyzed at a later time. Calculation of systolic and diastolic velocities and integration of the area under the curve (mean) were performed with a digitizing pad (Hitachi, Digital Graphics [USA], Inc, Sunnyvale, Calif) interfaced with a computer, without knowledge of the values for the other parameters.

Cardiac Output

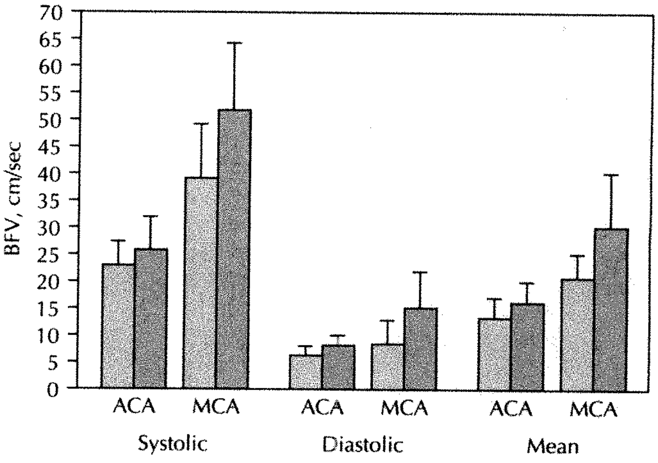
The technique used to determine CO has been previously described.[11] We positioned the transducer in the suprasternal notch and imaged the ascending aorta so that the angle of insonance with the direction of blood flow was always less than 15°, obviating the need for angle correction. We measured the peak BFV using Doppler ultrasound for at least five consecutive cardiac cycles just distal to the aortic valve. We integrated the systolic waveform to calculate the stroke distance (centimeters per beat) and averaged all values. We measured the ascending aortic internal diameter (d, trailing edge to leading edge)[13] at end-diastole in the transverse plane using M-mode echocardiography also just distal to the aortic valve. The cross-sectional area (A) was calculated as $A = \pi d^2/4$ (square centimeters). The stroke volume was determined by multiplying the stroke distance (centimeters per beat) by A (square centimeters). Cardiac output was then calculated by multiplying the stroke volume by the heart rate. We also calculated CO using a similar method described by Alverson et al,[12] who used the time-averaged BFV over the entire cardiac cycle rather than during systole alone, and therefore, included forward velocity during diastole. Although the second method yielded values that (as expected) were slightly higher than the first method, results were similar and all comparisons were identical. We chose to report the results of the first method because the SD was slightly smaller.

Ductal Patency

We determined the patency of the ductus arteriosus echocardiographically using standard criteria.[15] After imaging the bifurcation of the pulmonary artery in the parasternal view, we directed the Doppler transducer toward the left pulmonary artery and measured BFV. We considered anterior or retrograde velocity during diastole as evidence of a PDA.

Cerebral Vessels

We measured the BFV in the ACA and MCA bilaterally as described by Raju and Zikos.[8] After visualizing the ACA through the anterior fontanelle in the parasagittal plane, we measured the peak BFV using Doppler ultrasound at the genu of the corpus callosum. Care was taken to record the maximal velocity as determined by the audio and visual signals. We then visualized the MCA in the temporal transcranial view and measured the BFV 0.5 cm from the circle of Willis. For both arteries, the angle of insonance was always near 180°, with the direction of blood flow obviating the need for angle correction. We set the Doppler sample volume at 0.5 mm and the high pass filter at 100 Hz to minimize vessel wall motion. We determined the systolic and diastolic velocities and averaged values for at least five consecutive cardiac cycles. The mean velocity was determined by measuring the area under the curve of five consecutive cycles.



Blood flow velocity (BFV) in the anterior cerebral artery (ACA) and middle cerebral artery (MCA) on day 1 (solid bars) and on day 2 (shaded bars, P<.001 in all cases by two-tailed, paired t *test). Data are given as means±2 SDs.*

Interobserver variability was eliminated by having all the studies performed by the same individual. We evaluated intraobserver variability by comparing two determinants of all parameters obtained at the same time. The measurements consistently varied by less than 10%, as has been noted by others.[16]

Data were analyzed with paired and unpaired *t* tests, where appropriate, and differences were considered significant at $P<.05$. Data for CO, ductal shunting, and the intracranial vessels were determined separately without knowledge of the values for the other parameters. This study was approved by the Human Investigation Committee of our hospital.

RESULTS

All data are given as mean±SD. The average birth weight for the 23 newborns was 3.46±.60 kg, and they were studied at means of 7.6±2 and 30±3 hours following delivery. The heart rate, stroke volume, aortic diameter, and CO did not change significantly from day 1 to day 2 (Table 1). Thirteen newborns on day 1 had echocardiographic evidence of a patent ductus arteriosus, although none were symptomatic. The CO on day 1 for

Table 2.—Changes in Blood Flow Velocity (BFV) Related to Closure of the Patent Ductus Arteriosus (PDA)

	BFV Changes, cm/s (Mean ± SD)			
	Day 1	Day 2	*P**	95% Confidence Interval
Group 1 (n = 11)†				
Anterior cerebral artery				
Systolic	23.2 ± 5.1	26.2 ± 5.3	.006	1.0 to 5.1
Diastolic	5.8 ± 1.9	8.7 ± 2.4	<.001	1.8 to 4.0
Mean	13.3 ± 3.5	16.0 ± 3.7	.001	1.2 to 4.2
Middle cerebral artery				
Systolic	43.1 ± 12.5	56.3 ± 13.9	<.001	9.0 to 17.4
Diastolic	8.6 ± 3.3	17.1 ± 7.5	<.001	6.1 to 11.1
Mean	22.0 ± 6.5	33.5 ± 10.3	<.001	8.8 to 14.2
Group 2 (n = 10)†				
Anterior cerebral artery				
Systolic	23.8 ± 3.6	28.1 ± 7.7	.003	1.7 to 7.4
Diastolic	6.7 ± 2.1	8.2 ± 2.2	.032	0.1 to 2.8
Mean	13.8 ± 2.4	16.4 ± 4.1	.009	0.7 to 4.5
Middle cerebral artery				
Systolic	36.4 ± 6.5	49.6 ± 11.7	<.001	9.1 to 17.4
Diastolic	9.1 ± 3.3	13.6 ± 4.5	<.001	2.4 to 6.6
Mean	19.6 ± 3.6	28.0 ± 7.7	<.001	5.3 to 11.6

*Two-tailed, paired *t* test, day 1 vs day 2.

†In group 1, PDA open on day 1, closed on day 2; and in group 2, PDA closed on day 1 and day 2.

newborns with a PDA was not significantly different from those without a PDA (245±38 cm^3/kg per minute vs 261±61 cm^3/kg per minute) ($P = .45$, 95% confidence interval, −59 to 27). Only two newborns still had a PDA on day 2.

The left-sided and right-sided velocities in the ACA and MCA were combined for all analyses since there were no differences between them. For the entire group of newborns, the systolic, diastolic, and mean BFV in both arteries increased significantly ($P < .001$) from day 1 to day 2 (Figure).

In 11 newborns, a PDA was present on day 1 but not on day 2 (group 1). In 10 newborns, the PDA had closed by the first examination on day 1 and remained closed on day 2 (group 2). Two newborns who had a persistent PDA on day 1 and day 2 were excluded from further analysis. The systolic, diastolic, and mean BFV in both arteries increased significantly from day 1 to day 2 in both groups of newborns (Table 2). The magnitude of the increases on day 2 were not different between group 2 and group 1 ($P > .05$ by unpaired *t* test for all velocities).

COMMENT

Doppler ultrasound is a useful method of studying BFV in the ACA and MCA.[7-10] Measurement of the BFV in these arteries is reproducible if the probe position is standardized and the angle of insonance is minimized using real-time imaging.[17,18] Our values are comparable with those determined by other investigators using the same technique.[7,8] The close agreement between left-sided and right-sided velocities in our study adds further support to the reproducibility of this technique. The higher BFV in the MCA compared with the ACA has been consistently demonstrated.[11,13-16] Understanding the mechanism for the increase in BFV from day 1 to day 2 in the ACA and MCA is important to understanding the normal adaptation of the cerebral circulation to postnatal life. This increase in BFV either could result from changes in the systemic circulation or could be limited to local changes in the cerebral circulation.

Changes in CO could potentially be related to the observed increase in BFV. Doppler ultrasound has been shown to be a reasonable method of noninvasively determining CO in the newborn, especially when evaluating sequential changes in groups of patients.[7,11-14] Since probe position can be standardized with real-time imaging, the main source of error is in the measurement of the aortic diameter. We found that the mean diameter on day 1 was nearly identical to that on day 2. Consequently, we believe this measurement was sufficiently accurate to provide reliable sequential determination of CO, and our values are similar to those reported in the literature using this technique.[7,12,14] Our results agree with those of Wright et al[7] who demonstrated that CO remains stable from day 1 to day 2 and therefore cannot account for the significant increase in BFV that we observed.

Much has been written about the potential role of ductal shunting on cerebral perfusion in the premature newborn.[7,19,20] However, the effect of the PDA on BFV in the ACA and MCA in normal, full-term newborns has received limited study. Wright et al[7] demonstrated that newborns with a PDA on day 1 but not on day 2 had an increase in BFV in the ACA and MCA from day 1 to day 2. Our study differed from theirs in that our newborns were slightly older (7.6 vs 4.9 hours) for the first examination, which may account for why the PDA was closed in almost half of our patients on day 1. Since a significant increase in BFV occurred on the second day, irrespective of the presence of a PDA on day 1, we believe the increase in BFV on day 2 was not related to ductal closure. These newborns had a physiologic PDA and were asymptomatic. The relationship between ductal shunting and cerebral perfusion could be different for premature newborns with symptomatic ductal shunting.

Some authors have suggested that the increase in BFV may represent local changes in the cerebral circulation.

Either vasoconstriction at the site of insonation or vasodilation distally could result in an increase in BFV.[9,10] Fenton et al[9] performed a cross-sectional study in full-term newborns and attributed the higher BFV values in the older newborns to distal vasodilation because of a fall in an index (Pourcelot's) of vascular resistance. This index has not correlated well with vascular resistance in newborn animal studies.[21-23] In contrast, Drayton and Skidmore[10] have suggested that vasoconstriction at the site of insonation may be the mechanism for this increase in BFV. They speculated that vasoconstriction may be secondary to an increase in systemic blood pressure reflecting an autoregulatory phenomenon. However, the magnitude of the increase in blood pressure during this time is small (5% to 10%)[7,24] in contrast to the large (20% to 50%) increase in BFV. Consequently, it may be more likely that if vasoconstriction of these arteries occurs, it represents an early postnatal adaptation of vascular tone not necessarily related to changes in systemic blood pressure.

Currently, there are insufficient data available to explain the mechanism for the increase in BFV in the first few days following delivery in normal, full-term newborns. Although further study is required to delineate the mechanism, our data suggest this increase is not due to changes in CO or closure of the PDA.

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Headaches Preceded by Visual Aura Among Adolescents and Young Adults: A Population-Based Survey

Martha S. Linet, MD; Dewey K. Ziegler, MD; Walter F. Stewart, PhD
(*Arch Neurol.* 1992;49:512-516)

Children's Ice Hockey Injuries

Janny Dwyer Brust, MPH; Barbara J. Leonard, PhD; Alfred Pheley, PhD; William O. Roberts, MD

• *Objective.*—To determine the rate, type, and severity of injuries to child hockey players as well as assessing coaches', parents', and players' attitudes and knowledge of hockey.

***Design.*—A prospective observation of a population's injuries using injury-reporting forms and surveys.**

***Setting.*—A community-organized hockey program in Minnesota.**

***Participants:* One hundred fifty boys, aged 9 through 15 years, who played ice hockey during the 1990-1991 winter season.**

***Measurements and Main Results.*—Injuries were reported by multiple observers, including coaches, managers, and trained independent observers at the time an injury occurred; coaches, parents, and players were surveyed regarding hockey injuries, knowledge, and attitudes. One in three players experienced an injury during the season. The most common injuries were contusions. Six of 100 players experienced injuries severe enough to require cessation of physical activities for 8 to 25 days or longer. Weight differences of 53 kg and height differences of 55 cm were reported between Bantam-aged players (13 through 15 years), and body contact, including legal checks, accounted for 86% of injuries during games. Illegal checks and violations were associated with 66% of injuries during games, yet only four penalties (14%) were assessed. In addition, one in three games in which an injury resulted was described as hostile and 15% of the injuries were considered intentional.**

***Conclusions.*—Eliminating violence and body checking for prepubertal boys while emphasizing rule enforcement and good sportsmanship are recommended.**

(*AJDC.* 1992;146;741-747)

Ice hockey is a contact sport and participants are at risk for injury. Yet, the risk of injury for players at youth levels has received little study.

In recent years, escalating insurance costs coupled with hard body contact and violent game behavior have alarmed the hockey community. For example, in 1984, a Canadian study[1] reported an increase in the rate of cervical spine injuries. This study did a retrospective review of medical records from 1976 through 1983 of 42 spinal injuries that had been documented. In contrast, one spinal injury was documented from 1948 through 1974. Body checks that occur from behind a player, accompanied by collision with the boards, was the usual method of injury.[1] In addition, in 1987, a study of high school ice hockey players reported a rate of 75 injuries per 100 players. Head and neck injuries accounted for 22% of the total injuries.[2]

When ice hockey was compared with football in a study of catastrophic high school sports injuries incurred by players between 1982 and 1987, football contributed the most catastrophic injuries. However, football had fewer castastrophic injuries per 100 000 participants than did ice hockey or gymnastics.The rate of injury for ice hockey players was 2.55 per 100 000 in contrast to the rate of injury for football players of 0.68 per 100 000.[3] Of 530 catastrophic sports injuries assessed in Ontario in 1986,[4] hockey injuries led the list, with 25% of those injuries involving spinal damage.

Although the majority of hockey injury studies have concentrated on players of high school age and older, concern for younger players is growing. The Canadian Academy of Sport Medicine notes that serious injuries begin to appear in Peewee-level hockey players and asserts that body checking should not be allowed because of the differences in body size between players.[4] A Canadian study[5] that compared checking and no-checking leagues in Peewee-level players (ages 12 through 13) showed that 88% of fractures were related to body checking and that fractures were 12 times more frequent in players in leagues that allowed body checking. This study also reported that larger players were able to exert an impact force 70% greater than that exerted by smaller players.

These studies suggest that the risk for injury in youth hockey is high and that a major contributor is body checking. While checking is one form of body contact, the fighting that results from the violence allowed in the sport is another contributor to injuries. Injuries caused by fights have largely remained undocumented. However, the frequency of fighting is acknowledged by the Canadian Academy of Sport Medicine, who listed the elimination of fighting as one of their six recommendations.[4] In the United States, a study of Peewee-level players (ages 11 through 13) reported that of 52 games observed, fighting broke out about every third game. Players were reported to consider fighting a natural consequence of the game

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and exhibited a certain "resignation" about fighting (*Youth & Society*. December 13, 1981:229-244).

About 200 000 children play organized ice hockey in the United States, yet research and statistics on injuries is negligible. For example, the National Electronic Injury Surveillance System (NEISS) collects statistics on hockey injuries; however, records exist only on those children who were treated in hospital emergency departments, and not all hospitals were sampled. In the NEISS report,[6] ice hockey and field hockey are combined into a single hockey category. The NEISS report provides, at best, a very crude estimate of ice hockey injuries.

In Minnesota, ice hockey is a very popular sport with an estimated 30 000 children playing organized hockey under the auspices of the Minnesota Amateur Hockey Association. Again, information regarding injuries to these young players is acknowledged to be inadequate and unobtainable; however, each year, young players are injured playing organized hockey, some seriously.

One reason young players have not received attention is that a previous study reported a correlation between injury rates and age. Minor league players (ages 5 through 14 years) had an injury rate of one for every 100 hours of play or practice, compared with one injury every 7 hours for professional players.[7] Also, injury rates tend to be low for the youngest players because they do not have the speed or physical capacity to create damaging force with impact or to generate dangerous puck velocities. However, players as young as those at the Peewee level can reach speeds of 32 km (skilled, adult players can reach speeds of over 48 km) and puck velocities of up to 96 km (professional speeds have been recorded at 192 km).[8]

This study sought to understand the effects of age and body contact on injury by studying male hockey players who ranged in age from 9 through 15 years. This age range was selected to include younger children who are not in leagues that permit checking. This was a prospective study conducted during the 1990-1991 winter hockey season. The players were from a suburban community near the Minneapolis/St Paul area.

The major research questions were as follows: (1) What is the injury rate for young hockey players? What types of injuries are sustained? How severe are the injuries? (2) Is body contact associated with injuries (eg, checking, game infractions, fighting)? (3) Are other factors associated with injuries (eg, player position, size, age, game vs practice time)? (4) What do players know about hockey safety and what attitudes are held by players, parents, and coaches regarding injuries?

METHODS

Subjects and Procedures

The 150 subjects were children enrolled on nine teams that were organized by a community hockey league, including *Squirts* (ages 9 through 11), *Peewees* (ages 11 through 13), and *Bantams* (ages 13 through 15). Data were collected from November 23, 1990, until March 14, 1991.

Injuries were defined as any ice hockey or ice hockey–related injury that resulted in a player's not being able to continue to participate in a game or practice or that kept a player from participating in physical activities the following day. Also, all injuries to a player's face or head were reported. An injury severity rating based on the amount of time the child was limited from physical activity was used. This rating was similar to the one used by Gerberich et al,[2]—except that the category "minimal injuries" was included (Table 1).

Table 1.—Injury Severity Rating Scale

Rating	Time Required to Refrain From Physical Activities
Minimal	Remainder of the game or practice to 1 d
Minor	2-7 d
Moderate	8-24 d
Major	25 d or longer
Severe	Limb dysfunction, permanent joint dysfunction or amputation, organ loss
Catastrophic	Permanent disabling injury to central nervous system or death

Between one and five injury forms were collected on each player injured. Team managers and/or coaches received instruction on completion of injury forms. Trained observers were also hired to observe 139 games and practices that represented 21% of the total time spent on the ice by players. The trained observers completed injury forms independently. Players, parents, and coaches were surveyed about injuries and hockey knowledge and attitudes at the end of the season at various arenas. The survey response rate was 89% (134/150) for children, 82% (123/150) for parents, and 88% (21/24) for coaches. At least one coach per team participated.

Within a week after a report of an injury was received, a graduate research assistant, who was also a registered physical therapist, contacted the player's parents by telephone to verify the player's injury information. Parents were asked how long the child was kept from physical activities as a result of the injury. If a child was seen by a physician, parents were asked to sign a medical release form for review of the medical record.

Analysis

Descriptive statistics on injuries and hockey knowledge and attitudes are presented. Student's *t* tests and χ^2 tests were used to calculate differences on selected variables.

RESULTS

Injury Rates

Of 150 children studied, 52 injuries were reported from 44 players who experienced one to three injuries each (Table 2). Although 30% of the injuries involved more than one body part (eg, breaking a wrist and scraping the neck, a blow to the head and a strained neck), only the primary diagnosis is listed. Head, neck, and upper body injuries accounted for 46.3% of the injuries. The most common injuries were contusions (50%) (Fig 1).

In most cases (56%), disability, which resulted from the injury, lasted 1 day or less; however, nine players (17%) experienced injury that caused disability of 8 to 25 days or longer (Fig 2). These injuries were the result of four fractures (one to the wrist, two to the finger, and one to the collarbone), two contusions (one to the sternum and one to the collarbone), one sprained neck, one lacerated abdominal wall, and one dislocated shoulder. Thirteen injuries (25%) required medical care either in the emergency department or at a physician's office (Table 3). Forty-four (85%) of the injuries occurred during game situations, including scrimmages.

The season lasted 86 to 112 days, depending on a team's competitive level and playoff success. Teams typically had 73 ice hours (range, 53 to 97 hours), with slightly more practices than games. During games, an injury was experienced every 7 hours with a severe injury every 34 hours. During practice, an injury occurred every 44 hours.

Table 2.—Primary Diagnosis of 52 Injuries to 44 Hockey Players

Location of Injury	No. (%) of Injuries
Head and neck	
Blow to head	5 (9.6)
Neck strained	4 (7.8)
Neck sprained	1 (1.9)
Face abrasion	2 (3.9)
Total	**12 (23.2)**
Upper body	
Back contusion	5 (9.6)
Shoulder contusion	3 (5.8)
Shoulder dislocated	2 (3.9)
Collarbone fractured	1 (1.9)
Sternum contusion	1 (1.9)
Total	**12 (23.1)**
Trunk	
Contusion to ribs	3 (5.8)
Abdominal wall lacerated	1 (1.9)
Stomach contusion	2 (3.9)
Groin strained	2 (3.9)
Tailbone contusion	1 (1.9)
Total	**9 (17.4)**
Arm	
Arm contusion	2 (3.9)
Elbow contusion	2 (3.9)
Elbow abrasion	1 (1.9)
Wrist fractured	1 (1.9)
Finger fractured	2 (3.9)
Finger sprained	1 (1.9)
Finger contusion	1 (1.9)
Total	**10 (19.3)**
Leg	
Calf contusion	2 (3.9)
Knee abrasion	1 (1.9)
Knee contusion	3 (5.8)
Knee strained	1 (1.9)
Ankle sprained	1 (1.9)
Ankle contusion	1 (1.9)
Total	**9 (17.3)**

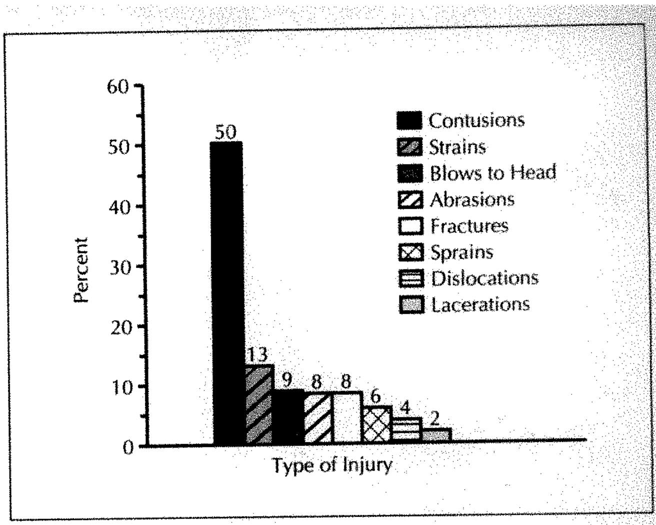

Fig 1.—*Type of injury (n=52).*

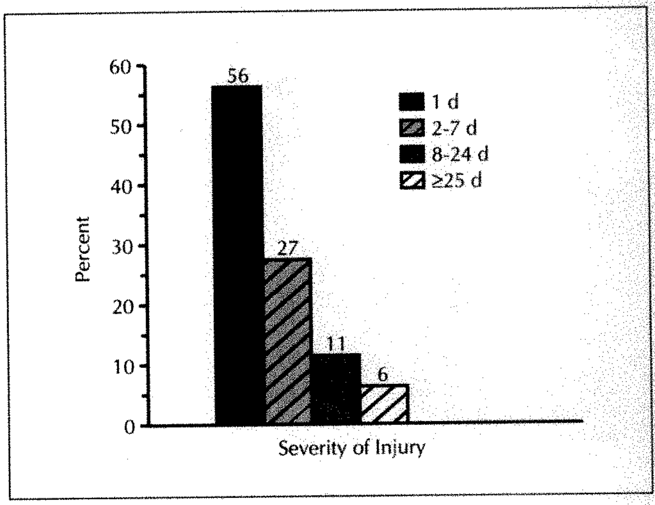

Fig 2.—*Severity of injury (n=52).*

Body Contact

The assessment of illegal checking and violations was made by the manager, coach, and/or trained independent observer who watched games and completed an injury form at the time an injury occurred. Body contact, both legal and illegal, accounted for 86% of all injuries that occurred during games (Table 4). Twenty-nine injuries (66%) were caused by illegal checking and violations but only four penalties (14%) were called. Four minor penalties (2 minutes) were assessed, and one player was assessed an additional 10-minute penalty for misconduct.

Of the four penalties called, all were at the Bantam level; three involved head and/or neck injuries and one involved a shoulder injury. Three of the four players were hit by another player. In all cases, players were assisted off the ice. The penalties assessed were for elbowing (n=2), checking from behind (n=1), and checking into the boards (n=1). These particular injuries were in the minimal or minor categories. Overall, the most common illegal check that resulted in an injury was when a player checked another from behind (n=5). The most common violation was elbowing (n=5).

Game Violence

Thirty-four percent of the games that resulted in an injury to a player were described as hostile (Table 4). Hostile games were defined as players calling each other names, players fighting, parents angry, and referee calls disputed. Friendly or neutral games were defined as those with no animosity expressed toward other team players, fans, or referees. A hostile game environment accounted for six of the eight injuries viewed as intentional, such as a player slammed after the whistle (which denotes the end of play) and a player kicked with a skate (Table 3).

Other Factors Associated With Injuries

Results of a Student's *t* test showed a statistically significant ($P=.02$) increase in injuries with age, with the most injuries sustained by Bantam-level players (54%) (Table 3). Players are placed on teams by skill level. "A" players exhibit the most skill and "C" exhibit the least. "A" players received the most ice time, yet "B" players had the most injuries (46%).

Injuries increased as the game progressed; most hap-

Table 3.—Injury Characteristics of 52 Players

Player and Game Factors	No. (%) of Injuries
Team	
Bantam	28 (54)
Peewee	14 (27)
Squirt	10 (19)
Skill level*	
A	9 (17)
B	24 (46)
C	19 (37)
Event	
Regular game	25 (48)
Tournament game	16 (31)
Scrimmage	3 (6)
Practice	8 (15)
Game period (N=44)	
First	6 (14)
Second	11 (25)
Third	20 (45)
Unknown	7 (16)
Game player position (n=44)	
Wing (n=2)	18 (41)
Defense (n=2)	15 (34)
Center (n=1)	8 (18)
Goalie (n=1)	3 (7)
Type of care	
Emergency room	10 (19)
Physician's office	3 (6)
None	39 (75)
Intentional harm	8 (15)
Hostile games	15 (34)

*A-level players exhibit the highest skill level; B-level players, medium-level skills; and C-level players, the lowest skill level.

Table 4.—Game-Related Injuries of 44 Players That Were the Result of Body Contact*

Injuries	No. (%) of Injuries
Legal checking	9 (20)
Illegal checking	17 (39)
Violations†	12 (27)
Total	**38 (86)**
Penalties called	4 (14)

*Includes injuries sustained during regular and tournament games and scrimmages.

†Three injuries involved one or more violations (only one was counted for this table) for a total of 32 violations.

Table 5.—Comparison of Body Size Between Bantam-, Peewee-, and Squirt-Level Players*

Player Level	Mean ± SD†	*P*‡
Bantam (n=40)		
Weight, kg	56 (37-90) ± 11.9	.0007
Height, cm	163 (133-188) ± 12.3	.05
Peewee (n=44)		
Weight, kg	45 (34-70) ± 8.9	NS
Height, cm	150 (120-170) ± 11.5	NS
Squirt (n=40)		
Weight, kg	34 (24-45) ± 5	NS
Height, cm	138 (105-158) ± 9.8	NS

*Children's reports were used because there were more children surveyed. However, Pearson correlations between parent and child report for weight was .81; for height, .63.

†Values in parentheses represent the range.

‡Significance is at $P \leq .05$; NS indicates not significant.

pened in the third period (45%). In 93% (41/44) of the games in which an injury occurred, the player was hit by another player, or the player hit something else. Sometimes the player was hit by more than one thing. Contact occurred most commonly with another player (n=26), followed by contact with the boards (n=8).

Injuries during practice were different from those during games. All practice injuries were minimal (player kept from physical activity for 1 day or less) or minor (player kept from physical activity for 2 to 7 days) and required no professional medical care. Goalies were most likely to be injured (37%), and contusions were the most common injury (88%). No head or neck injuries were reported.

Size differences among players increased with age, with Bantams showing the most variation. Between the smallest and largest Bantam player, a difference of 53 kg and 55 cm was reported (Table 5). Weight differences were statistically significantly different ($P=.0007$) for Bantams; lighter players were more likely to be injured. Injured players had a mean weight of 51 kg in comparison with uninjured players, whose mean weight was 63 kg.

Hockey Knowledge and Attitudes

Only half of the players at the Peewee and Bantam levels who had an average of 7 years' experience on hockey teams (range, 2 to 11 years) knew that checking from behind could cause another player serious injury or death. There was no difference in knowledge of this between Peewees and Bantams using a Student's *t* test. Twenty-six percent (11/42) of players who knew the seriousness of checking another player from behind, when queried, said they would do it (Table 6). For those who explained why they would check someone from behind, "being angry" and "getting even" were the most common reasons given.

Interestingly, only two thirds of the Peewee- and Bantam-level players said that they received instructions in "giving" and "taking" checks (Table 6). Fifty-five percent of the 129 players thought that their helmets and face masks protected them from all head and neck injuries. No significant differences by age level were found using χ^2 analysis.

When players were asked if they liked taking a check, only 28% answered yes. Yet players were the least interested in eliminating checking. In general, support for the elimination of checking at the Peewee level is limited and even less support exists at the Bantam level (Table 7).

Although all coaches responded that sportsmanship was "real important," only 59% of the players believed this. A χ^2 test showed statistically significant age-level differences ($P=.05$) with 76% (32/42) of the Squirts vs 45% (19/42) of the Bantams thinking that sportsmanship was "real important."

When parents, coaches, and players were asked which factors were "very important" vs "important" or "not important" in reducing injuries, rule enforcement received the highest rating from parents and coaches. Coaches, in contrast to players and parents, were the most likely to

Table 6.—Ninety Peewee- and Bantam-Level Players' Attitudes and Knowledge About Checking

Player's Attitude/ Belief	No. (%) of Players*
Checking from behind could result in:	
A player's getting killed or really hurt	42 (51)
A player's getting hurt but not very badly	30 (36)
Probably no injury	4 (5)
Don't know	7 (8)
Would check from behind knowing that a player may get killed or really hurt (n=42)	
Yes	3 (7)
Maybe	8 (19)
No	31 (74)
Likes checking others	65 (76)
Likes taking a check	21 (28)
Instructions received about checking	
On taking checks	60 (73)
On giving checks	62 (69)

*The percentage reflects the number of players who responded to specific questions.

Table 7.—Comparison of Players', Parents', and Coaches' Attitudes About Hockey*

Attitudes	No. (%) of Players	No. (%) of Parents	No. (%) of Coaches
Supports elimination of checking at Peewee level†	8 (10)	44 (57)	12 (57)
Supports elimination of checking at Bantam level†	2 (3)	19 (25)	2 (10)
Thinks sportsmanship is "real important"	78 (59)	NA	21 (100)
Factors that are considered as "very important" in reducing injuries			
Better medical care for injured players	61 (48)	52 (44)	7 (33)
Good sportsmanship	55 (44)	84 (72)	6 (29)
Better equipment	45 (35)	39 (33)	5 (24)
More rule enforcement	43 (33)	93 (78)	14 (67)
Grouping players within same skill level	41 (32)	55 (47)	7 (33)
More training for coaches	40 (31)	66 (55)	11 (52)
Stricter enforcement of rules	35 (27)	70 (57)	3 (14)
Players grouped by similar size	24 (19)	31 (26)	3 (14)
Eliminating checking	10 (8)	29 (25)	7 (33)

*Number of people surveyed was players, 134; parents, 123; and coaches, 21.

†Indicates that the question was asked of Peewee-level and Bantam-level players (n=84). The percentage reflects the number who responded to specific questions.

‡NA indicates that they were not asked.

think that the elimination of checking would reduce injuries, although only 33% thought this.

COMMENT

Injury Rate

This study showed 35 injuries per 100 players. This rate is lower than a previous study of high school players.[2] Squirts experienced the fewest injuries, and there were no serious injuries at the Squirt level, supporting the age association. There were six serious (8 to 25 days or more of disability) per 100 players. Interestingly, in 1989, NIESS estimated that there were 32.4 emergency department–treated injuries for 100 000 persons aged 5 through 14 during a 12-month period for all types of hockey players.[6] Results from this study provided higher estimates of seven emergency department–treated injuries per 100 players during a 4-month period, indicating that the national data have underestimated hockey injury rates. Our findings of an injury rate of one injury every 7 hours corresponds to Sutherland's[7] injury rate for professionals.

In a study with high school players,[2] 22% of the injuries involved the head and neck compared with 23% from this study. Contusions were the most common injury in both studies. These results suggest that young players appear to mimic the injury patterns of older players. Thus, potential for serious injury in young players is present.

It has been documented that players can achieve sliding speeds of 24 km.[9] Because a broken neck can occur at walking speed (5 km) depending on the force of impact, injuries to the head, neck, shoulder, back, and arm can potentially lead to a broken neck. In this study, those injuries accounted for 46% of the total. Our results, specifically those related to the number, type, and severity of injury, suggest that ice hockey is played in a very rough manner by young, amateur players, which puts them at substantial risk for severe injury.

There were no injuries to the eyes or teeth. Those injuries were of major concern in the 1970s before the mandatory rule requiring helmets and face masks was implemented. However, some researchers[2,10] believe that the increased protection for the face and head, while decreasing injuries to the eyes and teeth, may have contributed to the increase in injuries to the spine and concussions because players believe, mistakenly, that helmets and face masks make them invincible. Players' beliefs about invincibility were first reported by Tator and Edmonds[1] and were acknowledged by players in our study regardless of age level.

Body Contact

Checking and illegal game infractions by players accounted for 86% of all injuries incurred during a game, including every serious injury. Clearly, body contact, even within the proper context of the game, contributes greatly to injury to players. Considering that there is a difference of as much as 53 kg and 55 cm between players on Bantam teams, it is not surprising. Grouping players by weight, size, physical condition, skill, and physical maturation, rather than by age alone, had been suggested by many,[11,12] including the American Academy of Pediatrics.[13] Children, especially those aged 11 through 13, demonstrate differences from their peers that exceed 5 years in physiological age.[11] That is, when age alone is used to classify sports participation, children with physical builds that are similar to adult builds play collision sports with children who have not begun puberty.

Maturation influences not only a player's size and strength but many body systems, including the skeletal epiphyseal plate. The epiphyseal plate is most vulnerable during the growth spurt of puberty (average age 12 through 14 years); this makes the adolescent player more susceptible to injury than younger children.[11] The sexually mature adolescent with closed epiphyseal growth plates is at less risk for injury from contact and probably should not be competing with players who have open growth plates. Children under age 16 are still growing, and injury to their growth plates can cause serious, lifelong consequences. Although this study did not measure the sexual maturity of players, the vast differences in observed sexual development and size of a player add to the argument that checking should be eliminated through the Bantam level if players cannot be classified by physical maturation.

Support for checking is hard to understand. Regnier et al[5] not only demonstrated that checking increased the severity of injury to a player but showed that checking resulted in more penalties, particularly those of an aggressive or hostile nature. In addition, most players in our study admitted that although they liked giving checks, few liked taking them. Some in the hockey community feel that checking adds to the excitement of the game; however, considering the potential for injury and the inequities in players' sizes, this argument seems unreasonable. Because of concern for injury to a player, checking is not allowed at the Squirt level or younger and in many adult senior-level leagues. Nevertheless, because checking is allowed at the Peewee level, the Squirt-level players begin checking, even though it is not sanctioned. Forty percent of all injuries to Squirt-level players in this study were caused by checking; fortunately, none of those injuries was serious.

Rule Enforcement

Injuries that result from hard body contact (66% of which were deemed illegal), combined with lax rule enforcement, contribute to games that become increasingly hostile. A study of a Canadian children's team asserted that violence and rule infractions are built into the game and that players who want to excel must behave accordingly. The Canadian study reported that players received informal instruction in rule violation and on how to use illegitimate tactics.[14]

Nevertheless, coaches state that they believe sportsmanship is very important. Yet only 59% of the players believe that sportsmanship is very important, with older players believing it less. With 34% of the games that result in injury considered hostile—with the spectators, who mostly consist of players' parents, contributing to the hostility—it is not surprising that players are ambivalent about sportsmanship.

Nowhere is the practice of hockey violence more in evidence than in professional hockey, and 38% of the children in this study said they hoped to become professional players. Young hockey players observe professional hockey players and mimic their violent behavior. The resulting impact on a child's moral development and psychological health cannot be positive.

The need for referees to enforce rules is nothing new. Many authors[2,3,10,15] have called for rule enforcement. However, this study shows that very few penalties were called for injuries incurred during games. It is recommended that referees be made more aware of the injuries that are involved in a loosely controlled game. In this study, parents and coaches viewed the enforcement of rules as being the most important factor in reducing injuries.

Education

Children were more likely to be injured in games than in practices. However, because practices are sometimes less supervised than games (eg, less attention is paid to wearing equipment, more "fooling" around occurs with pucks and sticks), serious injuries are a possibility even though none occurred during this study period. Therefore, safety rules, including wearing the proper equipment, should be enforced during practice whether the child is playing inside or outside. Independent observers reported that players sometimes practiced without helmets or other required equipment.

Our results showed that only half of the Peewee- and Bantam-level players understood the seriousness of checking another player from behind, and worse, some of them were still willing to do it. Checking from behind is life-threatening, therefore *all* players must be educated about hockey maneuvers that involve serious threats to others' safety. Stricter rules that call for progressive penalties or the eviction of players or teams for the season who continue to check others from behind or endanger other players should be considered. Liability concerns alone should support this consequence.

An integral part of any hockey program that is geared for children should include information on prevention of injuries, including strengthening neck muscles. The Canadian Amateur Hockey Association distributes a brochure describing these exercises.[10]

Studies have demonstrated that cervical spine fractures most often occur when the crown of the head strikes the boards, goalposts, or another player while the neck is partially or fully flexed.[10,15] Therefore, players should be taught "heads up" hockey like they are taught "heads up" football.[15] In other words, players should avoid hitting anything with their heads, especially the crown of the head. Players should also be reminded that their helmets do not make them invincible, that their necks and their opponents' necks are very vulnerable.

Although this study's results are similar to other reports, results should be viewed with caution since these results represent one season and one community. Injury reports, however, appear to be reliable. Very little discrepancy existed in the injury or game information provided by coaches, managers, parents, players, or independent observers. However, it should be noted that the injuries in this study were not verified by a physician or trainer, with the exception of the injuries that required medical intervention. Although this limits the validity of the injury report, it is also reflects the environment of community-organized leagues where trained medical professionals are not available on site, with the exception of tournament games. These conditions make collecting injury data at the youth level much more difficult than at the high school and college level, where trained professionals can evaluate athletes almost daily and would know if a player refrained from physical activities for 1 day or more. We tried to increase the reliability and validity of the game and injury information by collecting data prospectively, by reviewing medical records when possible, by enlisting several trained reporters, and by surveying parents and players at the end of the season. Nevertheless, it is probable that minor injuries were underreported. Injured players sometimes leave the ice on their own, and coaches may not see the child for several days; therefore, a minor injury could go unnoticed.

The study of minor injuries is important, especially those involving the head and neck, because they may be precursors to more serious injuries. The impact that size and sexual maturity of a player have on injury also requires further study. This study used self-reported weights and heights. It would be preferable in future studies to calculate actual weights and heights and to use Tanner's stages[16] as a measure of sexual maturity. In addition, longitudinal data with larger populations are recommended to put these study results in perspective. Nevertheless, the results of this study indicate that the hockey community needs to consider changes for the protection of its young players. Eliminating checking, promoting sportsmanship, enforcing rules, and educating players, coaches, referees, and parents are some areas to pursue.

Although the majority of hockey injuries in children are minor, injuries occur frequently and there is a risk of serious injury to a child. With this in mind, it is imperative that current game rules are enforced. In addition, players and coaches need to receive more education on preventing hockey injuries. Because of extreme differences in players' sexual maturity and size, which increases the risk for injury, checking should be eliminated if team selection is based on a player's age alone. The need for an ongoing record of national statistics for hockey injuries is needed to fully understand the scope of the problem.

Finally, communities should work together to remove the violence from children's games. Parents, coaches, and players who act in a violent or hostile manner should not be tolerated. Those who are given warnings and continue the behavior should be removed from the premises. If a player is assaulted before, during, or after a hockey game, parents should consider filing criminal charges against the other player. Behavior not tolerated in other settings should not be tolerated in hockey.

Hockey is an exciting, fun game for children. Agility, speed, hand-eye coordination, and intellectual processing are all used to the highest degree. Fighting and excessive body contact are not necessary parts of the game and detract from skill-building. Eliminating unnecessary game risks that endanger the health of children while emphasizing the skills and fun of ice hockey should be of utmost importance.

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Electroencephalographic and Behavioral-State Studies in Infants of Cocaine-Addicted Mothers

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• *Objective.*—To evaluate cerebral cortical function with electroencephalography in infants of cocaine-addicted mothers.

***Design.*—Patient series.**

***Setting.*—The Children's Hospital of Philadelphia (Pa).**

***Participants.*—Thirty-five consecutive infants of cocaine-addicted mothers hospitalized for a comprehensive health assessment and 51 healthy, age-matched infants studied with electroencephalography and respiratory thermistor because they were siblings of sudden infant death victims (comparison group).**

***Interventions.*—None.**

***Measurements/Main Results.*—Behavioral states during spontaneous daytime sleep were classified as active sleep or quiet sleep; quiet sleep was further characterized as immature, tracé alternant sleep or mature, continuous, slow wave sleep. No episodes of ictal apnea or nonictal apnea were recorded in infants of cocaine-addicted mothers; nonictal apnea was observed in one control patient. No electrographic seizures were recorded. There were no significant differences between the proportions of infants exposed to cocaine in utero and that of controls who displayed excessive sharp electroencephalographic transients, background abnormalities, immaturity, and hypermaturity. Electroclinical sleep discordance was present in 5.7% of infants of cocaine-addicted mothers vs 0% of controls. Cocaine-exposed infants displayed mature, continuous, slow wave sleep below 45 weeks of conceptional age in a significantly higher percentage than those in the comparison group.**

***Conclusions.*—Although frank electroencephalographic abnormalities were infrequent in infants whose mothers were addicted to cocaine, they differed significantly in their younger age of onset of continuous, slow wave sleep. Our findings provide continued reason for concern that infants of cocaine-addicted mothers may suffer subtle adverse neurologic, cognitive, or behavioral effects later in life. The longitudinal assessment of sleep disturbance and its relation to later development might permit tracking of the long-term effects of prenatal exposure to cocaine.**

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The use of cocaine has become an alarming social problem, and cocaine is the drug of greatest public health concern in the United States. It is estimated that up to 8 million Americans use cocaine regularly, and that 5% to 20% of these individuals are seriously dependent.[1] The increase in the use of cocaine by the general population has been paralleled by a similar increase among pregnant women.[2]

Cocaine use during pregnancy has been associated with increased risks of spontaneous abortion and fetal death, intrauterine growth retardation, and low Apgar scores.[3-9] Newborns exposed to cocaine in utero are also at a greater risk of neonatal problems such as respiratory distress syndrome, congenital malformations, and necrotizing enterocolitis.[3] Of greatest concern are neonatal central nervous system disorders such as smaller head circumference, abnormal behavior,[6-9] cerebral infarction or hemorrhage,[10,11] seizures,[7,12] and sudden infant death syndrome (SIDS).[1,6,13]

Previous studies examining the brain function of cocaine-exposed newborns using electrophysiologic means are scarce and have shown conflicting results.[14-17] This study evaluates cerebral cortical function using electroencephalography (EEG) in infants born to cocaine-addicted mothers (ICAMs) to clarify the prevalence of EEG abnormalities in this population and to analyze the effects of prenatal exposure to cocaine on short-term maturation of brain function, as evaluated by the developmental chronology of behavioral state patterns.

PATIENTS AND METHODS

Patients

We describe our experience with 35 consecutive ICAMs (18 boys and 17 girls), with a mean estimated gestational age (EGA) of 38.3 weeks (range, 29 to 41 weeks) and a mean conceptional age (CA) of 42.7 weeks (range, 36 to 56 weeks). Conceptional age is determined by adding the age since birth to the EGA. All the

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Table 1.—Clinical and Electroencephalographic (EEG) Data of Infants of Cocaine-Addicted Mothers (ICAMs) and of a Comparison Group*

	EGA, wk	CA, wk	Gender Ratio, M/F	Ictal Apnea	Nonictal Apnea	Abnormal EEGs	Excessive SETS	Background Abnormalities	Immature EEG	Hyper-mature EEG	Clinical-EEG Discordance
ICAMs (n=35)	38.3 (29-41)	42.7 (36-56)	1:0	0	0	5 (14.3)	2 (5.7)	0	0	1 (2.8)	2 (5.7)
Comparison group (n=51)	38.4 (30-43)	42.6 (34-52)	1:7	0	1 (2.0)	4 (7.8)	1 (2.0)	2 (4.0)	1 (2.0)	0	0

*EGA indicates estimated gestational age; CA, conceptional age; and SETS, sharp EEG transients. Data are expressed as mean (range) for EGA and CA, and number (percentage) for the rest of the categories.

infants had been exposed to cocaine in utero. Seven infants were exposed to heroin, six to alcohol, four each to methadone hydrochloride and marijuana, and one each to amphetamine, diazepam, and barbiturate. Maternal drug use was determined first by personal interviews in a safe and private environment by experienced interviewers; in addition, maternal and neonatal urine toxicologic assays were performed in all study subjects. Urine screening for cocaine metabolites was performed with immunoassay (enzyme-modified immunoassay technique) and confirmed with gas chromatography and mass spectrometry. Routine screening of urine for other drugs was performed with thin-layer chromatography; positive test results were confirmed with immunoassay.

All patients had an unremarkable neonatal course without significant pathologic conditions that could have compromised the brain function (eg, asphyxia, intracranial bleed, seizures, and sepsis).

A comparison group was chosen from a population of infants referred for a comprehensive health assessment because they were siblings of victims of SIDS. The Infant Apnea Program of The Children's Hospital of Philadelphia conducts a comprehensive medical, cardiorespiratory, and neurologic evaluation of infants who have experienced apnea and siblings of victims of SIDS.[18] The comparison group was selected to represent healthy-appearing siblings of victims of SIDS. The results of their physical and neurologic examinations were normal, and the battery of laboratory tests, such as a complete blood cell count, measurement of serum electrolyte levels, chest roentgenogram, electrocardiogram, thermistor pneumocardiogram studies, and EEG, showed no abnormalities. Each patient was otherwise healthy and neurologically well. This group included 51 newborns, 32 boys and 19 girls, with a mean EGA of 38.4 weeks (range, 30 to 43 weeks), who were evaluated at a mean CA of 42.6 weeks (range, 34 to 52 weeks).

All the mothers of the infants included in the comparison group denied drug use during pregnancy.

Informed consent was obtained from parents or guardians of the study infants.

Electroencephalography

Electroencephalograms were recorded in the laboratory or at the patient's cribside (mean postnatal age, 4.3 weeks; range, 1.5 to 9 weeks) with a 21-channel Grass electroencephalograph. All EEG recordings were performed between 8 AM and 4 PM. An array of 12 surface electrodes was applied to the scalp with electrode paste according to the International 10-20 System modified for neonates.[19] Sixteen channels were devoted to the EEG and five recorded polygraphic features, including electro-oculogram, electrocardiogram, and nasal and chest respirations. The duration of EEG recordings ranged from 30 to 60 minutes. The technologist made frequent notations of small and large body movements, skin color changes, apnea, and rapid eye movements. Behavioral states (awake, active or rapid eye movement sleep, quiet or non–rapid eye movement sleep, and indeterminate sleep) were recognized using standard criteria.[20] Quiet sleep was further characterized as (1) immature, tracé alternant, identified as bursts of high-voltage (50 to 200 μV), bilaterally synchronous δ and ϑ activity separated by low-voltage (less than 25 μV) interburst periods; or (2) mature, continuous, slow wave sleep (CSWS), identified as continuous moderate- to high-amplitude (50 to 150 μV) slow activity (1.5 to 5.0 cycles per second), in which sleep spindles may arise.[20]

All EEGs were reviewed by one of us (R.R.C.) and analyzed for objective abnormalities.

1. Excessive sharp EEG transients were defined as more than 20 sharp EEG transients per 10 minutes of a sample of active sleep).[21]
2. The EEG background patterns were classified as normal or mildly, moderately, or severely abnormal, according to well-established criteria.[22]
3. The EEG background patterns were judged abnormally immature or hypermature if background cerebral activity implied a CA that was at least 3 weeks younger or older than the CA determined by maternal dates or Dubowitz examination.[18]
4. Presence of ictal or nonictal apnea was determined. Prolonged apnea has been previously defined by the American Academy of Pediatrics Task Force as "cessation of breathing for 20 seconds or longer, or as a brief episode associated with bradycardia, cyanosis or pallor." Ictal apnea was defined as a definite electrographic seizure clinically accompanied by apnea. Nonictal apnea was recognized as a cessation of breathing in the absence of electrographic seizure patterns.[18]

Behavioral state was analyzed for discordance between clinical and electrographic sleep state, and maturity of sleep measured by the age at onset of CSWS.

Statistical Analysis

The number of infants who displayed EEG or sleep state abnormalities was compared between study patients and infants in the comparison group with χ^2 analysis. The χ^2 analysis also compared the number of ICAMs displaying EEG or sleep abnormalities among the subgroups of infants exposed to cocaine alone or to multiple drugs, and among the subgroups of infants exposed to cocaine at different trimesters in utero. The EGA and CA were compared between ICAMs with and without EEG abnormalities using the unpaired Student's *t* test. Differences were considered significant at *P*<.05.

RESULTS

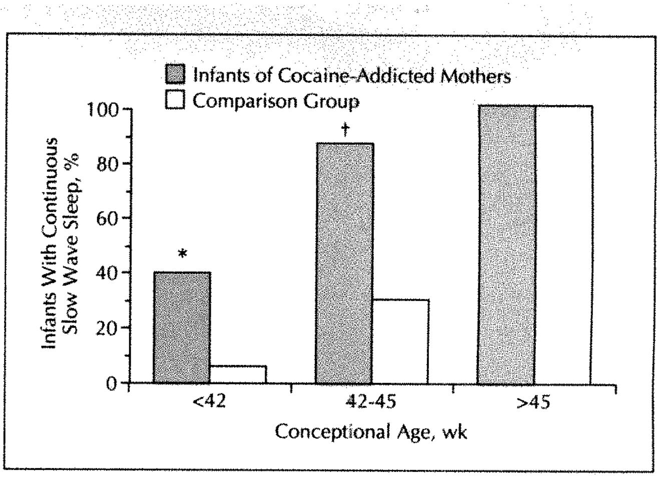
Of the 35 cocaine-addicted mothers, 26 (74.3%) used cocaine throughout the entire pregnancy, four (11.4%) during the first trimester, two (5.7%) during the second and third trimester, two (5.7%) during the first and second trimester, and one (2.9%) during the third trimester. Four ICAMs (11.4%) displayed symptoms of withdrawal during the neonatal period, according to the Neonatal Abstinence Score System developed by Finnegan[23]; only one required symptomatic drug treatment. Infants of cocaine-addicted mothers and infants of the comparison group did not differ in the duration of the EEG recordings.

Table 1 displays the patients' EGA, CA, gender ratio, and EEG data. Infants of cocaine-addicted mothers did not differ from the comparison group with respect to EGA or CA. Male-female ratio was 1.0 in ICAMs and 1.7 in the

Table 2.—Electroencephalographic (EEG) Abnormalities and Continuous, Slow Wave Sleep (CSWS) in Infants of Cocaine-Addicted Mothers According to Type and Duration of Drug Exposure*

	Normal EEG	Abnormal EEG	CSWS Present	CSWS Absent
Type of drug exposure				
Cocaine only	17	2	9	10
Multiple-drug abusers	13	3	12	4
Duration of drug exposure				
Throughout pregnancy	22	4	17	9
Other trimesters	8	1	4	5

*Differences are not statistically significant. Data are expressed as numbers of infants.



Age at onset of continuous, slow wave sleep in infants of cocaine-addicted mothers and in a comparison group of healthy, age-matched infants. Asterisk indicates $P<.05$; *dagger,* $P<.01$ *vs comparison group.*

comparison group. No episodes of ictal apnea or nonictal apnea were recorded in ICAMs; nonictal apnea was observed in one comparison group patient. There were no significant differences between the two groups with respect to the presence of excessive sharp EEG transients, background abnormalities, or dysmaturity of EEG patterns. No definite electrographic seizures were recorded in any of the patients. Two ICAMs, but none of the comparison group, showed signs of clinical-EEG sleep state discordance ($P=.08$) (Table 1).

Infants of cocaine-addicted mothers with normal EEGs had a mean (±SD) EGA of 38.9±2.4 weeks and a CA of 43.3±3.9 weeks, whereas in those with abnormal EEGs, EGA was 34.6±4.3 ($P<.01$) and CA was 39.4±3.2 ($P<.05$). Electroencephalographic abnormalities were not related to the duration of drug exposure in utero ($P>.05$) or to maternal multiple drug use ($P>.05$) (Table 2).

Most of the infants showed cycling between wakefulness and different sleep states. Sleep was not recorded in one infant. In six ICAMs, sleep state persisted as active (rapid eye movement) throughout the recording. A quiet (non–rapid eye movement) sleep state was observed in 28 ICAMs (seven with tracé alternant and 21 with CSWS). Six (29%) of the 21 infants with CSWS displayed well-formed sleep spindles.[20] The Figure shows the age dependence of "maturity of sleep" in ICAMs and infants in the comparison group as measured by the percentage of infants with CSWS. The two groups differed significantly in this measure of sleep behavior: the respective percentages of ICAMs and infants in the comparison group with CSWS were determined according to CA as follows: younger than 42 weeks, 40% vs 6% ($P<.05$); 42 to 45 weeks, 85.7% vs 31% ($P<.01$); and older than 45 weeks, 100% vs 100% ($P>.05$). The presence of CSWS in ICAMs was not influenced by the time of drug exposure in utero ($P>.05$) or by maternal multiple drug use ($P>.05$) (Table 2).

COMMENT

Neurologic complications are a major concern for infants exposed to cocaine in utero. Perinatal cerebral infarction[10,12] and intracranial hemorrhage[10,11] have been well documented with head ultrasound[10,11] or computed tomography.[12] The prevalence of neurologic abnormalities is significantly greater in ICAMS than in normal infants.[10] The most conspicuous clinical findings include seizures, restricted brain growth, and disturbed behavior. Clinical seizures within 36 hours of delivery, unrelated to structural brain damage, have been reported as an important complication in ICAMs.[7,12] Head circumference is smaller in ICAMs than in control infants.[3,5,7] On the Brazelton Neonatal Behavioral Assessment Scale, infants exposed to cocaine in utero have a significant reduction of interactive behavior and a poor organizational response to environmental stimuli.[6-8]

Although the dramatic effects of stroke, intracranial hemorrhage, and seizures only occur in a small fraction of ICAMs, there is substantial concern that important, but subtle, alterations may operate in others. It is desirable to seek simple, reliable, objective tools of neurologic assessment in those who lack overt signs of a severe acute encephalopathy. Electrophysiologic techniques are ideal for this role.[14-17] In our study, we examined cerebral cortical function in ICAMs and found only 14.3% with any type of EEG abnormalities at a mean CA of 42.7 weeks, which was not significantly different from the incidence in an age-matched comparison group. Few studies have reported EEG findings in ICAMs. Brown et al[16] studied 19 infants of drug-dependent mothers and found EEG abnormalities (electrographic seizures and excessive sharp activity) in six (50%) of 12 of those exposed to both narcotics and cocaine. Doberczak et al[17] performed EEGs in infants exposed to cocaine alone in utero and found abnormalities in 17 (45%) of 38 during the first week of life; but EEG abnormalities persisted after 3 months in only one infant. Neither study used a control or comparison group. Contrary to these reports,[12,16,17] we did not confirm the presence of excessive sharp waves or seizures in ICAMs. Moreover, in our study, ICAMs with EEG abnormalities had significantly lower EGAs and CAs than ICAMs with normal EEGs, suggesting that gestational or perinatal factors other than cocaine exposure could account for the difference.

The mechanisms by which in utero cocaine disturbs fetal neurologic integrity are complex and inadequately understood. Some effects might be explained on the basis of the pharmacologic action of the drug. Cocaine passes transplacentally from mother to fetus.[24] Incomplete biotransformation of cocaine by placental cholinesterases also yields active metabolites that expose the fetus to toxicity.[25] Cocaine is sympathomimetic; it inhibits the reuptake of norepinephrine and dopamine at adrenergic nerve endings,[26] and may induce embryofetal systemic vasoconstriction, which could result in perinatal cerebrovascular accidents.[10,11] Neonatal seizures in ICAMs can be secondary to infarction, hemorrhage, the prolongation of cerebral catecholamine action, or a direct neuronal toxic effect.[12] Studies in adults have shown that cocaine increases EEG amplitude,[27] β rhythms,[28] and ϑ activity,[29] which may be related to the development of clinical seizures. In experimental animals, cocaine facilitates the development of "kindling"[30] and promotes the spread of epileptiform discharges in subcortical limbic structures.[31] The different behavior of human postnatal EEGs after cocaine exposure could be explained on the basis of less bioavailability of cocaine due to increased placenta catabolism near term[25] or cessation of cocaine exposure after delivery.[17] Neonates whose mothers used cocaine 1 to 2 days before delivery excrete cocaine metabolites in the urine for as long as 96 hours[17]; none of our study infants were excreting cocaine at the time of the EEG, since none was performed before age 1 week.

We did not record any apnea in our study group, although ICAMs are believed to be at a higher risk of SIDS.[6,13] Previous studies have shown that the majority of infants at risk for SIDS without a history of drug exposure have normal EEGs.[18] The absence of significant EEG abnormalities in ICAMs suggests that in this population, central nervous system cortical dysfunction also plays no important role in the pathogenesis of SIDS.

The abnormal neurobehavior exhibited during the neonatal period in humans[6-8] and rodents[32-34] exposed to cocaine in utero might be related to its action on catecholaminergic[26] and cholinergic[35] systems, which are relevant to neuronal development.[7,32,33,35] Grimm[36] hypothesized that such interference could initiate compensatory neurochemical mechanisms that would partially correct for the abnormalities but still impair the infant's ability to cope with complex environmental demands later in life. Studies using dopamine-specific ligands to visualize the receptor proteins for the dopamine system show alterations in binding. This indicates that developmental exposure to cocaine, although not altering monoamine content or morphology, nevertheless perturbs central dopaminergic function.[32,37] Furthermore, cocaine-exposed offspring may exhibit an attenuation in dopamine activity that may be relevant to hyperactivity and attentional deficits.[32]

Behavioral-state regulation and organization reflects central nervous system integrity.[38] Sleep is the predominant behavioral state of the neonate.[39] Sleep during the neonatal period is orchestrated by well-developed cyclicity.[40] The neonatal ultradian sleep cycle is approximately 40 to 60 minutes[41] and most newborns exhibit a complete sleep cycle within this time, as most of our infants did during their EEG monitoring. Recent studies in fetal sheep have shown that cocaine decreases the percentage of rapid eye movement (active) sleep,[42] and polysomnographic studies in human newborns have found that in utero cocaine affects the percentage of time of wakefulness and decreases the amount of quiet sleep, indicating an alteration in postnatal sleep organization.[38] Our study assessed the maturity of quiet sleep determined by the presence of CSWS, a valuable index of brain maturation.[39,40] In ICAMs, there was a tendency to show electroclinical sleep discordance, and the frequency of early acquisition of a mature pattern of quiet sleep (CSWS) was significantly higher than in the comparison group before conceptional age 45 weeks. Electroencephalographic recordings were performed at the same time of the day in ICAMs and in infants of the comparison group; therefore, it is unlikely that circadian clustering of sleep periods could account for the differences. The higher percentage of ICAMs with a mature, quiet sleep pattern during routine duration of EEG recordings strongly indicates hypermaturity, as ICAMs spend less time in quiet sleep,[38] and short-term monitoring would decrease the possibility of detecting it. The significance of precocious maturity of quiet sleep is unclear. This behavioral state is modulated by the infant's biologic maturity at birth.[43] Therefore, an early maturation of quiet sleep may indicate accelerated biological development. The neurochemical basis underlying this process is not well known. The physiologic mechanisms governing quiet sleep and active sleep lie in the pontine reticular formation and are modulated by acetylcholine, serotonin, and norepinephrine.[39,44] During periods of wakefulness, the activity of aminergic (inhibitory) neurons is high, and, reciprocally, the activity of the cholinergic neurons is low. During quiet sleep, aminergic inhibition gradually declines and cholinergic excitation increases; active sleep occurs when the shift is complete.[44] It is possible that among cocaine's neurochemical effects on the developing central nervous system[32,33,35] is accelerated maturation of the sleep pattern. Cocaine alters norepinephrine metabolism within the locus ceruleus, an important site that modulates sleep.[45]

Accurate and quantitative measurement of substance abuse is a complicated issue faced by clinical investigators when trying to determine the effects of drugs on the fetus.[46,47] This study shares the same limitations as other clinical investigations of infants born to drug-addicted mothers. Specifically, the potential confounding influences of socioeconomic status, race, poor prenatal maternal care, diet, and other unrecognized factors are difficult to measure.[46,47]

Our results support the presence of behavioral-state abnormalities in ICAMs.[38] Although the small sample sizes reduce the power to detect important differences, such behavioral-state abnormalities do not differ between infants exposed to cocaine only or to cocaine plus other drugs (Table 2). These results suggest that cocaine is probably the major contributor to our findings. As sleep state psychophysiology reflects nervous system integrity, sleep alterations in ICAMs reflect a disturbance of brain function.[38,40,42] It is unclear whether these sleep disturbances continue beyond the neonatal period. Studies that have evaluated the psychomotor development of ICAMs during the first months of life have raised questions about their behavioral and neurocognitive outcomes.[47-49] In agreement with other authors,[10,32,36,38,40-42,47-49] our findings also provide grounds for continued concern that ICAMs may have a *subtle* adverse neurologic, cognitive, or behavioral impact later in life. The study of sleep-wake state organization in premature infants has shown that those variables that reflect disrupted sleep predict future psychomotor performance.[43] Prospective polysomnographic sleep studies in a larger population of ICAMs are warranted. The longitudinal assessment of sleep disturbance in ICAMs and its relation to their later development might permit tracking of the long-term effects of prenatal exposure to cocaine.

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The Persistent Parent

William W. Waring, MD

• Parental persistence in the diagnosis and treatment of a child's illness can be examined by asking whether it is congruent with the child's morbidity. The relationship between parental persistence and child morbidity always depends on a "first diagnosis" (ie, what is wrong with the child, if anything?). In many instances, a "second diagnosis" (ie, why is the child being brought to you at this time?) should not be overlooked. First and second diagnoses are identical if persistence and morbidity are congruent but are different if they are incongruent. Once incongruent persistence is suspected, the possibility of parental falsification of symptoms must be faced. In patients in whom a second diagnosis must be made, the second diagnosis may be as simple as maternal anxiety or as complex as Munchausen syndrome by proxy. A "persistence algorithm" is presented and illustrated by descriptions of four children referred to a pulmonologist with complaints suggestive of respiratory disease. The approach, as outlined in the algorithm, may have broad pediatric applications.

(*AJDC.* 1992;146:753-756)

Thirty years ago, Yudkin,[1] a consultant-pediatrician in London, England, published a simple clinical paper called "Six Children With Coughs: The Second Diagnosis." His point was that when a child is brought to a doctor two different diagnoses can often be made. These diagnoses are the answers to two questions: (1) What is the matter with the patient? and (2) Why is this child being brought for care at this moment? The answer to the first question is taught in medical schools and during residency training, whereas the ability to answer *both* questions, in his words, is "the beginning of real medicine."

The first diagnosis in each of Yudkin's coughing children was recurrent respiratory tract infections, but the second diagnoses were different. In one, the mother wanted support in an ongoing fight with her mother-in-law about her care of the child. In another, because the child sweated at night, the mother needed assurance that her child did not have tuberculosis, although she did not mention this fear. Other cases were examples of hidden anxieties or parental manipulation. However, case 6, a "little boy" excessively kept home from school by his mother because of minor respiratory infections, was different from the first five cases. His case will be considered later.

Yudkin's children set me thinking about the second diagnosis and especially a factor common to all six that can be called the "persistent parent." In almost all instances, however, it is the mother who persists. Such persistence can be fully expressed during a first encounter or it may emerge gradually over months or years. The problem faced by the physician in dealing with persistence is to decide on its *congruence* with the reported symptoms and clinical findings, ie, the relation of the second diagnosis to the first diagnosis. The resulting pivotal decision may be essential if the physician is to help the patient.

Following are case descriptions of children recently referred to me as a pulmonologist for treatment of respiratory problems. A "persistence algorithm" (Figure) is introduced by means of which the clinician may approach the problem of incongruent parental persistence.

PATIENT REPORTS

PATIENT 1.—John, now 4½ years old, was having recurrent pneumonia. Shortly after birth, esophageal atresia and tracheoesophageal fistula were successfully repaired. His postoperative course included pneumothorax and evidence of esophageal leakage. At age 9 weeks he developed the first of 13 cases of pneumonia for which he was usually hospitalized.

When weaned from bottle to cup, his mother noted that he often coughed while drinking liquids but not while eating solids. Results of barium esophagograms and esophagoscopy were normal, without esophageal stenosis, aspiration, or gastroesophageal reflux. Treatment included oral and nebulized albuterol sulfate, chest physical therapy, and administration of repeated courses of antibiotics.

On examination, John was eupneic and cough-free. His weight and height were at the 5th percentile for age. His lungs were clear on auscultation, and his fingers were not clubbed. When offered water to drink, he frequently and immediately coughed. A review of numerous chest roentgenograms brought in by his mother showed infiltrates in the right upper lobe and

Department Editor.—*Alan D. Bedrick, MD*

Purpose.—*This department is intended to provide current information on clinical and scientific pediatric medical advances and analyses of current controversies in pediatrics. Pediatric Perspectives is a medium to provide insights and innovative ways of viewing pediatric medical topics, including novel approaches to difficult or common issues. In addition, discussions of present-day forces and issues that affect the everyday practice of pediatrics by all physicians, from the general practitioner to the teacher/clinician to the research scientist, are pertinent.*

Editorial Comment.—*We have all cared for patients who present with a "first diagnosis," yet clearly have a "hidden agenda" or "second diagnosis" that is really the underlying issue. The second diagnosis may or may not even be conscious to the parent, thus making clinical problem-solving that much more challenging! The algorithm provided by Dr Waring permits a sound clinical approach to this vexing clinical dilemma.*

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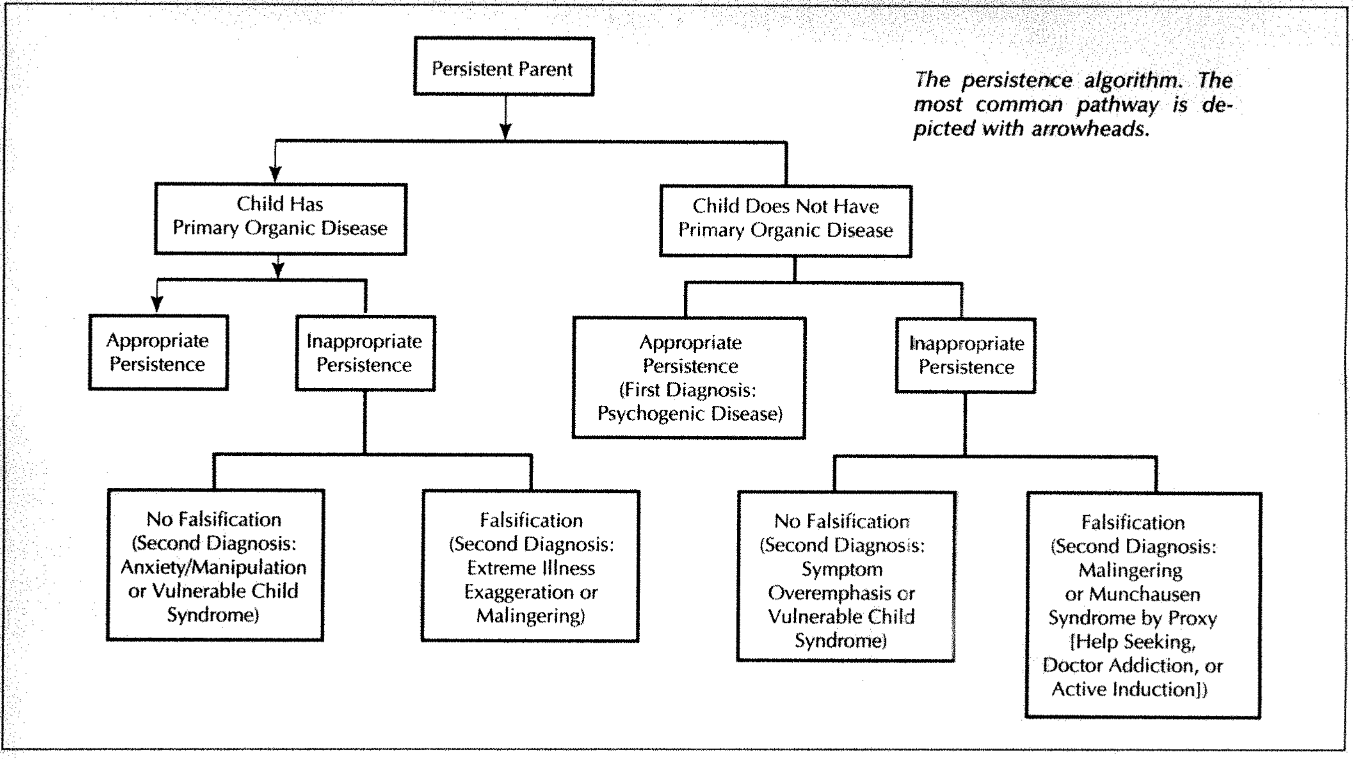
Persistent Parent
Child Has Primary Organic Disease
Child Does Not Have Primary Organic Disease
Appropriate Persistence
Inappropriate Persistence
Appropriate Persistence (First Diagnosis: Psychogenic Disease)
Inappropriate Persistence
No Falsification (Second Diagnosis: Anxiety/Manipulation or Vulnerable Child Syndrome)
Falsification (Second Diagnosis: Extreme Illness Exaggeration or Malingering)
No Falsification (Second Diagnosis: Symptom Overemphasis or Vulnerable Child Syndrome)
Falsification (Second Diagnosis: Malingering or Munchausen Syndrome by Proxy [Help Seeking, Doctor Addiction, or Active Induction])

The persistence algorithm. The most common pathway is depicted with arrowheads.

left lower lobe, with a persistent middle lobe atelectasis that had lasted for many months.

On John's second visit, a barium esophagogram was performed by a pediatric radiologist with John drinking a very thin barium mixture while standing. On at least 10 of the swallows, barium was observed to leak into the upper trachea at the level of the larynx. No tracheoesophageal fistula, either at the site of the original fistula or elsewhere, was seen.

When John's mother was told that he was aspirating for unknown reasons, she was excited and happy. She "knew something was wrong" all along, and her persistence had been rewarded, although the diagnosis and treatment were still unclear. Laryngoscopy by a pediatric otolaryngologist later revealed a small posterior laryngeal cleft. Several weeks later the cleft was successfully closed with endoscopic surgery. Coughing promptly ceased, and no subsequent cases of pneumonia were reported.

Clearly, John had a significant, potentially life-threatening, organic disease (documented pneumonias requiring numerous hospitalizations). These pneumonias were caused by aspiration of feedings through a laryngeal cleft (the first diagnosis) that had previously eluded detection. His mother's persistence in seeking an answer was commensurate (congruent) with John's morbidity, as was her joy that the search was nearing an end and that he might well be cured. In Yudkin's sense, the first diagnosis and the second diagnosis were the same.

Patient 2.—Harold, age 16 months, referred because of numerous apneic episodes, had been connected to an apnea monitor since birth. (At age 12 days, his older sibling had had a cyanotic episode requiring resuscitation; cardiorespiratory monitoring of this sibling was discontinued at age 14 months after a 2-month, alarm-free period.) Although a pneumogram obtained shortly after Harold's birth was interpreted as normal, he was discharged from the nursery with continued surveillance by the monitor at his parents' request. His first apneic episode occurred at age 13 days, and others followed, usually ending with tactile stimulation. A second pneumogram at age 8 months was normal. However, shortly thereafter Harold had more frequent apneic episodes, some of which required mouth-to-mouth resuscitation. A third pneumogram at age 13 months was interpreted as abnormal. A pediatric cardiologist ordered Holter monitoring for 24 hours. Although there were isolated unifocal premature ventricular contractions, Harold's heart was pronounced normal. At age 14 months, a 24-hour pH study of the esophagus showed gastroesophageal reflux, but a course of metoclopramide hydrochloride and bethanechol chloride had no effect.

Two weeks before his visit, pulse and respiration were absent for 4 minutes, during which his mother employed cardiopulmonary resuscitation. By the time of his visit, he was having 15 to 20 episodes of apnea each night, some of which required mouth-to-mouth resuscitation. Nothing in his history suggested asthma, croup, or pneumonia.

Family history revealed that his older sibling (described above) had repeated grand mal and petit mal seizures that could not be controlled despite the efforts of a neurologist. These seizures were spontaneously outgrown 2 months after Harold's birth. Three cousins on the maternal side, all with the same mother, had died in infancy of apnea. Harold's father was a baggage handler whose shift at the airport ended at midnight, or occasionally later. Almost all of Harold's episodes occurred before his father returned home.

On physical examination, Harold was a well-appearing but fussy infant. Scattered inspiratory and expiratory wheezes could be heard, mainly in the right lung. A chest roentgenogram showed some suggestive linear densities extending into one of the bases. The most recent pneumogram was reviewed and reinterpreted as being within normal limits. Results of polysomnography and simultaneous pH monitoring of the esophagus showed no significant apneic episodes or abnormal degree of gastroesophageal reflux. Several weeks of event recording showed no significant apnea or bradycardia.

After a discussion with a pediatric psychiatrist, a meeting was scheduled with the parents without Harold. It was pointed out that (1) the maternal history of multiple apneas could not be reconciled with the recently completed laboratory studies without postulating faulty monitoring equipment or parental observation, and (2) if inaccurate conclusions were being based on faulty observations, then unnecessary, expensive, and possibly injurious diagnostic testing and treatment would follow. It was recommended that Harold's life be normalized as soon as possible with discontinuation of apnea monitoring and with frequent supportive visits to the local pediatrician. In the presence of the family, the circumstances were reported by telephone to the child protection authorities. (The agency later declined to act in the absence of any physical evidence of abuse.) The family failed to appear for a second scheduled visit. Several months later, a telephone call to the family pediatrician for follow-up revealed that the apnea monitor had been discontinued, no further apneic episodes had occurred, and Harold was doing well.

This is an example of Munchausen syndrome (MS) by proxy[2] in which a parent, usually the mother, invents or induces disease in her child for no obvious reason. The absence of primary organic disease is often difficult to prove in the face of convincing assertions to the contrary from an apparently devoted mother. The problem in these cases is further complicated by occasional erroneous interpretations and by minor or gray-zone abnormalities that frequently eventuate from numerous diagnostic studies, eg, central apnea on pneumograms, premature ventricular contractions, wheezes on auscultation, and streaky densities on chest roentgenograms. In Harold's case the history and the morbidity were strikingly incongruent. All information about the illness was from the mother alone, and her testimony could not be confirmed with prolonged monitoring.

The neurologist who had treated Harold's sibling revealed that he had found no organic basis for the seizures and had concluded that they were an instance of MS by proxy. Information tangentially obtained also suggested that Harold's mother herself had MS.[3] For many months, she had severe seizures (in one of which she broke her leg) that did not respond to medications but that resolved spontaneously. In light of the poor prognosis for MS by proxy,[4] it is difficult to believe that Harold's (or his mother's) problems were totally resolved. It must be concluded that Harold had little or no significant organic disease (no first diagnosis) and that his mother's persistence, compounded with falsification for no apparent reason, was pathologically incongruent (second diagnosis of MS by proxy).

Patient 3.—Mary, aged 10 years, was referred by her pediatrician because of intractable cough of 3 weeks' duration. A loud and "barking" cough had begun with a typical upper respiratory infection and was thought at first to be viral croup. Numerous visits to her pediatrician led to trials with various antibiotics, topical nasal steroids, cough suppressants, antihistamines, albuterol by metered-dose inhaler, intramuscular betamethasone, and oral prednisone. Chest and sinus roentgenograms were normal. Examination by an otolaryngologist revealed no apparent cause for the cough, and new medications, including a tapered-dose trial of oral methylprednisolone and inhaled beclomethasone, had no effect. Cough persisted, with as many as 10 episodes each minute, but was absent during sleep. School attendance had been severely interrupted. No similar episodes had previously occurred.

Patient history revealed that Mary had been delivered prematurely and required intubation and mechanical ventilation for 10 days, although she had no known pulmonary sequelae. Her mother and stepfather had full-time jobs. Mary, her stepfather, and a stepsister of about Mary's age got along together very well. Mary was an honor student and enjoyed school.

On examination, Mary was extremely cooperative and knew every detail of her illness and the various medications she had received. The only abnormality was a frequent "barking" or "honking" cough, so loud that conversation could not take place while she was coughing. Results of spirometry, both before and after inhalation of albuterol, were normal and showed no postbronchodilator improvement.

Two large rolls of elastic bandage were obtained, and Mary was told that her cough would surely respond to strapping of her chest. However, the bandages had to be worn continuously until all coughing had ceased. She was asked to call or write to report on how the chest wrapping had worked. In Mary's absence, her mother was told that Mary had a habit cough and that in almost all cases the cough would respond to the tight chest wrap. Also, a brief exploration of family and school dynamics with the mother at this time revealed no obvious psychologic basis for the cough.

Follow-up by telephone to the mother's office revealed that the cough had immediately improved and had disappeared completely in 4 days. A letter from Mary dated 12 days after her visit confirmed this information.

Although Mary's psychogenic cough (the first diagnosis) was not organic in cause, her mother's persistence was congruent with the symptoms. In a sense, it was thrust on this working mother by the ceaseless and demanding nature of the symptom. The second diagnosis was the same as the first.

Untreated, such coughs may persist for months. The approach used in Mary's case has been described by Cohlan and Stone,[5] who used a bedsheet to strap the chests of their patients. Lavigne et al[6] have recently described a different technique called "reinforced suggestion" in the successful treatment of four patients with psychogenic cough.

Patient 4.—Anthony, 11 years old, sat in his mother's lap during much of the interview. He was referred by an otolaryngologist for evaluation of recurrent nasal staphylococcal infections.

His illness began 5 months earlier with low-grade fever, sore throat, intermittent headaches, and pharyngeal symptoms interpreted as postnasal drip. Several antibiotics were administered, but symptoms did not improve. *Staphylococcus aureus* was repeatedly cultured from the nasopharynx. Three months after onset of symptoms, results of computed tomography of the sinuses were normal. An infectious disease consultant found no significant infection. Two months before the visit, because of persistent low-grade fever and continued presence of *S aureus* in the nasopharynx, another course of antibiotics was administered, again without apparent effect. Weight gain had been satisfactory throughout the illness. His temperature, measured twice daily by his mother, rose to about 37.2°C almost daily. Highest recorded temperature during the illness was 38°C.

Patient history indicated that at age 3 years, and again at age 10 years, he had maxillary sinusitis that was radiographically confirmed on both occasions. Anthony had a vocabulary of 1000 words at age 1 year. He was in sixth grade and on the honor roll, but avoided sports. Anthony's mother, a housewife, had had severe sinusitis that required a Caldwell-Luc operation. She expressed the belief that there was something wrong with his liver, possibly hepatitis.

Anthony appeared thin and slightly pale. Physical findings were limited to partial occlusion of the left naris. Results of tests and examinations performed on the day of his visit were normal for chest roentgenography, sedimentation rate, serum immunoglobulin concentrations (including IgG subclasses and IgE), levels of liver enzyme in serum, and presence of hepatitis antigens and antibodies in serum. Anthony's parents were reassured that there was no risk to his health at that time. Cessation of routine measurement of temperature was recommended. It was also suggested that Anthony engage in a full range of school activities, including sports.

It was unclear whether Anthony had organic disease, although the possibility of mild rhinitis existed. A chronic *S aureus* nasal carrier state without morbidity seemed likely. Maxillary sinusitis had definitely occurred but was ruled out with results of computed tomography in the presenting illness.

Regardless of whether true primary organic disease was present, the maternal persistence here was curiously incongruent. The algorithm (Figure) helps sort out what may have happened. If there is no organic disease and maternal persistence is incongruent, one must ask if there is some reason to believe that falsification of the history is taking place. Although a vocabulary of 1000 words at age 1 year strains belief, there were no clear-cut falsifications of Anthony's illness history. Had there been such, the probable second diagnosis in Anthony's case would have been a less common form of MS by proxy called Doctor Addiction. Libow and Schreier[7] have postulated three forms of parental action in MS by proxy: the Active Inducer, the Doctor Addict, and the Help Seeker. Most extreme is the Active Inducer. In this case, the patient is usually an infant whose physical health or life is threatened. Doctor Addiction, a milder expression of MS by proxy, usually involves an older child whom the parent cannot physically abuse without risk of exposure. The Doctor Addict, usually the mother, is obsessed with the goal of obtaining medical treatment for nonexistent disease but does not go beyond lying about symptoms and signs. The child in the Doctor Addiction category "goes along" with maternal prevarication because of a pathologic maternal attachment and, in a sense, is in collusion with her. The risk is more to the child's integrity than to the child's person. The mildest form of MS by proxy is the Help Seeker, in which the mother invents disease in her child as a pathetically inappropriate means of getting help for some real problem. The motivation of the Help Seeker is understandable, and the problem ceases when the needed aid arrives.

If Anthony did have organic disease even of a mild type (as he did when younger), we can return to the algorithm for help. If the maternal response is incongruent, then the question of falsification again arises. If there is no falsification, one is dealing with an anxious or manipulative parent—or perhaps an instance of Vulnerable Child syndrome.[8] If there is falsification or extreme embellishment of illness details, the condition may be Extreme Illness Exaggeration.[9] This entity resembles the Doctor Addiction form of MS by proxy, differing chiefly in that true, albeit mild, organic disease exists. The diagnosis of MS by proxy need not be limited to instances in which primary organic disease is absent. It should include parental inflation or exaggeration of symptoms of mild disease.

How to classify Anthony? It was concluded that he had no organic disease (no first diagnosis) and that his mother's incongruent persistence did not involve falsification. The algorithm leads one to a second diagnosis of what can be termed *Symptom Overemphasis*, a state in which the parental search continues for the cause and cure of minor complaints that might in another family be ignored by both child and parent as "background noise." The search is incongruent, but does *not* involve falsehood.

COMMENT

Yudkin assigned no second diagnosis to his case 6, the "little boy" whose mother sought every means available to keep him out of school. His "Six Children With Coughs" was written 16 years before Meadow[2] described MS by proxy. Because organic disease (recurrent respiratory infections) existed in the boy and the mother's persistence was excessive in relation to (incongruent with) his symptoms, was the second diagnosis parental anxiety/manipulation (no falsification), Extreme Illness Exaggeration (falsification), or a variant of the Vulnerable Child syndrome? Information is insufficient to make the necessary distinctions. Yudkin did not consider the possibilities of a mother who lies or physically abuses her child covertly.

Application of the persistence algorithm begins with a nearly subconscious decision by the physician that this parent is attaching *much* more weight to these symptoms than do other parents. Many referrals to subspecialists result from dogged parental demands that may or may not be justified. Persistence is a spectrum, and in certain instances its absence constitutes negligence. Given what seems great parental persistence, one must ask if its degree is commensurate with the morbidity. Obviously, the more serious, dramatic, or prolonged the symptoms, the more pronounced should be the parental persistence, whether or not those symptoms can be related to organic disease. Assaying the congruence of persistence and morbidity requires a first diagnosis: What is wrong with this child—if anything? Incongruent parental persistence is always a sign of unease, the cause of which the physician is obligated to seek in making a second diagnosis.

The algorithm cannot be used until a history, physical examination, and probably some ancillary studies have been completed. Most children presenting with symptoms have organic disease, and their parents are congruently concerned (persistent), as were the mothers of patients 1 and 3. When organic disease exists but the degree of parental persistence seems excessive (incongruent), Yudkin's second diagnosis is needed. Each of his patients' parents, with the possible exception of case 6, can be classified as anxious or manipulative, or perhaps their cases were instances of the Vulnerable Child syndrome. Here, a little sleuthing can usually unearth the second diagnosis and alleviate the parent's unvoiced concern. On the other hand, deliberate enlargement of the disease by lies, as noted in some mothers of asthmatic children,[9] can require months and the efforts of a skilled medical team to suspect and confirm.

A few patients with persistent parents have little or no organic disease. It is this group of children that constitutes a particularly vexing problem for physicians whose anger and frustration may occlude their view to the all important second diagnosis. When parental persistence is congruent, the child frequently has a factitious disease of one type or another, eg, psychogenic cough (patient 3). However, when there is no primary organic disease, the parent is persistent, and falsification exists, MS by proxy in one of its forms is usually the second diagnosis (patient 2). Just as in Extreme Illness Exaggeration, the diagnosis and treatment of MS by proxy can be exhausting and frustrating. The case of patient 4, who had no organic disease and whose mother was incongruently persistent, but apparently telling the truth, is probably an example of symptom overemphasis. Clinical experience and the logic of the algorithm suggest such an entity.

In treating patients with persistent parents, the physician should be alert to differences between the first diagnosis and the second diagnosis, especially when a first diagnosis is absent (ie, when the first diagnosis is a "well child"). Although here exemplified by patients presenting with pulmonary complaints, the persistence algorithm can be applied to the entire field of pediatrics. This is especially true when the relation of symptoms and primary organic disease is difficult to define (eg, gastroenterologic conditions). At least, the algorithm provides a means of considering the entities whose common characteristic is parental persistence and, consequently, a means of dealing with the second diagnosis.

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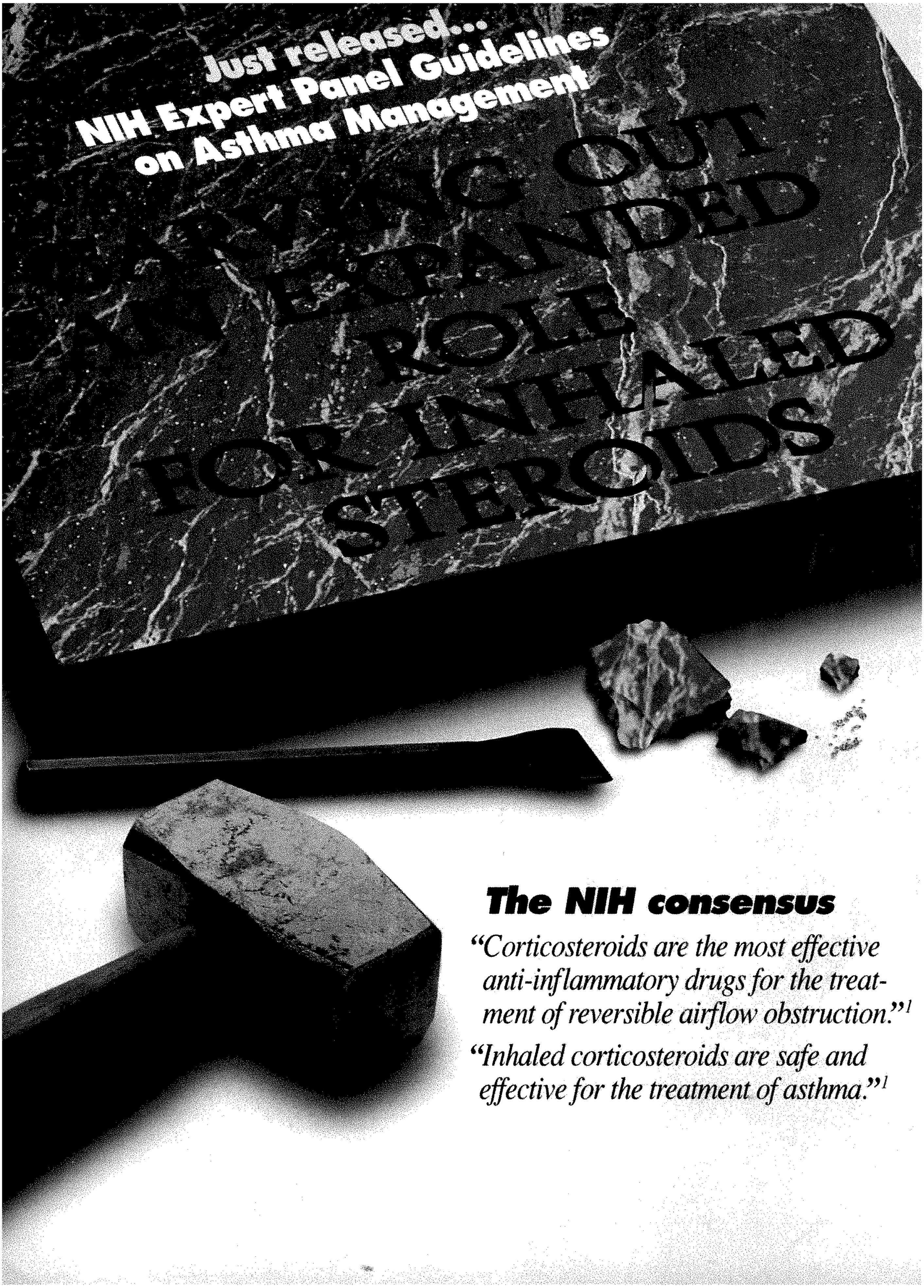

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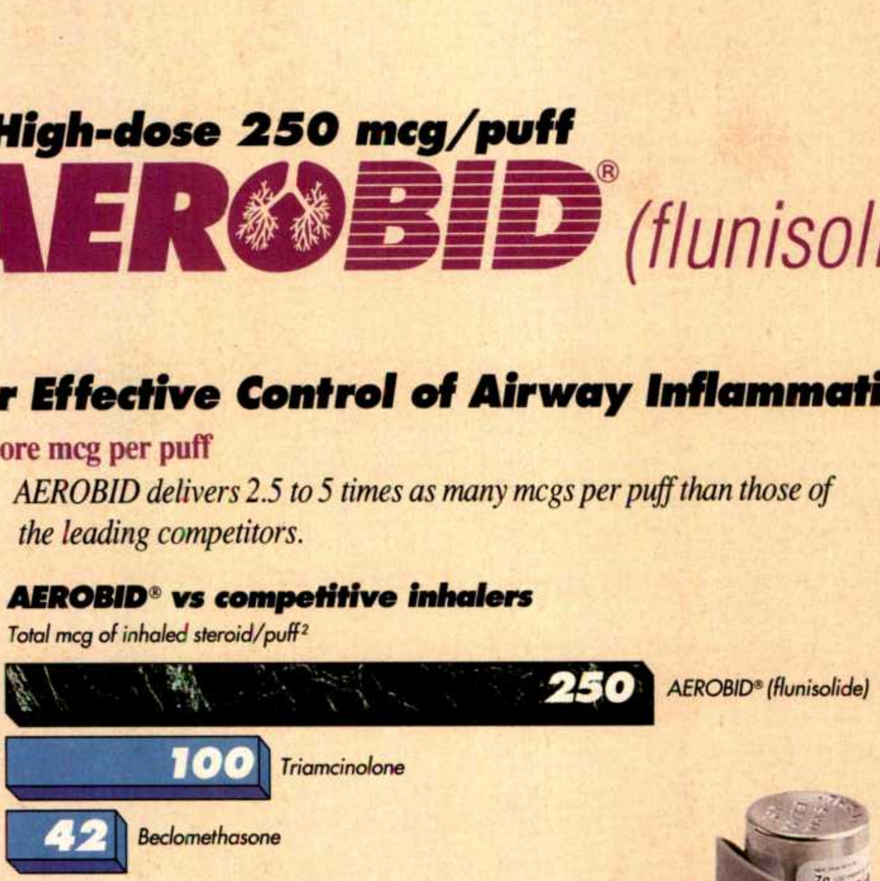

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Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with Candida albicans or Aspergillus niger have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral Candida may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler.

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function.

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice. An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors.

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General:* flu (10%); *Mouth and Throat:* sore throat (20%); *Nervous System:* headache (25%); *Respiratory:* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); *Special Senses:* unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations; *Gastrointestinal:* abdominal pain, heartburn; *General:* chest pain, decreased appetite, edema, fever; *Mouth and Throat:* Candida infection; *Nervous System:* dizziness, irritability, nervousness, shakiness: *Reproductive:* menstrual disturbances; *Respiratory:* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*; *Skin:* eczema, itching (pruritus), rash; *Special Senses:* ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; *Cardiovascular:* hypertension, tachycardia; *Gastrointestinal:* constipation, dyspepsia, gas; *Hemic/Lymph:* capillary fragility, enlarged lymph nodes; *Mouth and Throat:* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; *Nervous System:* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo; *Respiratory:* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort; *Skin:* acne, hives, or urticaria; *Special Senses:* blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath.

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*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

CAUTION: Federal law prohibits dispensing without prescription.
For full prescribing information, please see package insert.

(NDC 0456-0672-99)

Mfd by: Riker Laboratories
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2. *Physicians' Desk Reference®.* 45th ed. Oradell, NJ: Medical Economics Co Inc; 1991:955, 1862, 2026.

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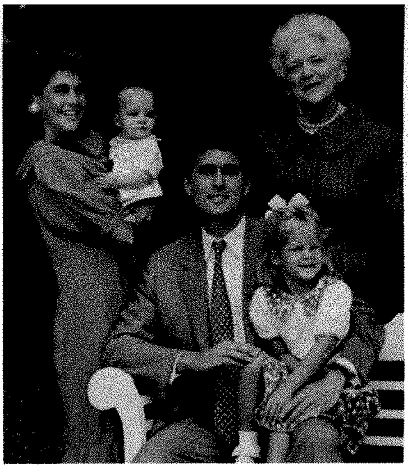

ULCERATIVE COLITIS CAN STRIKE ANY FAMILY.

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The Psychologic Fallout From Chernobyl

E. Richard Stiehm, MD

An epidemic of monumental proportions has stricken the children of the Ukraine—a direct aftermath of the nuclear power plant accident at Chernobyl on April 25, 1986. As many as 75% of the children of the Kiev area were affected. The result is considerable anxiety, multiple clinic visits, and prolonged hospitalizations (2 to 6 weeks). The general population is outraged, politicians are calling for action, physicians are responding with countless diagnostic tests and therapeutic maneuvers, parents are sick with worry, and, as usual, the children are suffering the most. Despite all of this concern and activity, the epidemic shows no sign of abating and, instead, is getting worse.

What disease is this, where did it come from, what is its cause, and what is its cure? The disease, according to the Ukrainian doctors, is "vegetative dystonia." Its origin is said to be the nuclear power plant accident, which released low levels of radiation—in the air, in the food, and in the soil. The result is an imbalance of the vascular tone of the circulatory system (controlled by the involuntary or autonomic nervous system); and its management and cure are complex and not entirely satisfactory.

The symptoms include fatigue, pallor, inattention, abdominal pain, headache, and poor school performance. The clinical findings include pallor; swollen lymph nodes; enlarged thyroid gland; and cool, clammy extremities. The diagnosis is readily made based on clinical evidence alone, but special laboratory tests are used to determine the particular clinical form of dystonia so that the right form of treatment is given. These special tests include rheoencephalography (a procedure to test the blood pressure of the jugular veins), interval electrocardiography (modified electrocardiography to analyze the heart's intrinsic rhythm), and whole-body thermography (to map alterations of surface temperature of the skin). These tests are not used in Western medicine to diagnose any illness.

Treatment is long and complicated and usually involves admitting the child to one of the 14 pediatric hospitals in Kiev. There are about 4000 beds in pediatric wards in Kiev for an overall population of 2.5 million, a much greater number of beds for the pediatric population than in any Western country. As many as 25% of hospitalized children (up to 1000 children) have vegetative dystonia; some pediatric wards have special units for patients with vegetative dystonia. The children are hospitalized for 4 to 6 weeks and treated with vitamins, immunostimulants, vasoconstrictors, vasodilators, and physical therapy. After a while, they are pronounced improved or cured and sent home, often to return for further therapy. The parents are distraught and angry, particularly when told that their child has secondary effects of radiation; their anger is directed at the government of the former Soviet Union 500 miles north in Moscow that built and ran the nuclear reactors.

I first encountered this elusive epidemic during a Greenpeace–Soviet Union–sponsored visit to Kiev in June 1991 to meet pediatricians, give lectures about immunology, and examine the children of Chernobyl. I was totally unprepared for my encounter with vegetative dystonia because it was not described in my (or their) textbook of pediatrics, nor were my physician hosts able to give me a medical article about the problem. Thus, the clinical picture was nonspecific, the diagnostic tests were simplistic, and the treatment was of doubtful efficacy and possibly harmful (6 weeks' hospitalization is known to have adverse psychologic effects on almost any child).

Vegetative dystonia most closely resembles "chronic fatigue syndrome" (CFS), a mysterious disease affecting many individuals in the United States.[1] Chronic fatigue syndrome has been associated with conditions such as chronic viral infection, excess yeast in the system, and environmental allergy. Here, also, the symptoms are vague, the results of laboratory tests are indefinite, and the treatment is of dubious value. Many physicians are skeptical about CFS, and rarely make this diagnosis. Others promote CFS enthusiastically, diagnose it frequently, and have a cadre of worried patients who undergo multiple laboratory tests and expensive therapies. Stephen E. Straus, MD, of the National Institutes of Health, in a recent review article,[2] pointed out that CFS has existed since 1750 under different names, including febricula (1750), neurasthenia (1825), effort syndrome (1871), chronic brucellosis (1934), hypoglycemia (1974), and total allergy syndrome (1985). The characteristic setting in almost all cases is an anxious patient (or in this case a parent), a convinced doctor, and a minor or major precipitating event. Thus vegetative dystonia is CFS by proxy, assigned to the children by parents and doctors.

The situation in the Ukraine is ripe for an epidemic of this sort. Most Ukrainian parents are justifiably uneasy

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From the UCLA Department of Pediatrics.
Reprint requests to UCLA Department of Pediatrics, 10833 Le Conte Ave, Los Angeles, CA 90024-1752 (Dr Stiehm).

about the radiation from Chernobyl and worry constantly about their children's minor complaints. When these are brought to medical attention, their doctors blame the radiation disaster and start finding all the manifestations of vegetative dystonia, invariably present to a greater or lesser degree in all children. The aggravating crisis was the current political turmoil of the country, with its sluggish economy, the denial of religious freedom, and restriction of ethnic self-determination by the central (Moscow) government.

The local pediatricians seem unable to cope with this complex crisis. They are rapidly trained, poorly paid, and overworked. The authoritarian nature of Soviet medicine did not lead to a diversity of opinion as to the cause and nature of any illness. Access to journals, medical libraries, and conferences and contact with outside physicians was minimal. To illustrate the degree of medical isolation, I noted that not one of the 300 or so of the doctors I met knew the outcome of the bone marrow–transplant experience of Robert Gale, MD, in Chernobyl,[3] although all knew he had been there.

Thus, the Ukrainian doctors unanimously believe in vegetative dystonia; they have convinced worried parents that their child's vague complaints are serious and require extensive diagnostic tests and prolonged hospitalization.

I examined a dozen children hospitalized with vegetative dystonia and witnessed the laboratory tests performed. I found all children but one to be absolutely normal on physical examination; the one with abnormal results of examination had a rare genetic syndrome, myositis ossificans progressiva, not related to radiation exposure. This lack of organic disease among the Chernobyl victims was also noted in a recent United Nations International Atomic Energy Agency report.[4]

The vegetative dystonia epidemic is occurring too many years after the Chernobyl explosion to blame it on acute radiation exposure; and it is occurring too soon to believe it is an early manifestation of the cancers that will occur in some of the people severely exposed. It does not develop in individuals receiving high-dose radiation treatment. Thus, it is the psychologic fallout of the accident, occurring at a unique period of social unrest. The solutions will not come from medical investigations (except to exclude organic disease), but from physician education and parental reassurance. The medical response to date is not part of the solution, but it *is* a good part of the problem!

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In Other AMA Journals

ARCHIVES OF GENERAL PSYCHIATRY

A Family Study of Obsessive-Compulsive Disorder

Donald W. Black, MD; Russell Noyes, Jr, MD;
Risë B. Goldstein, MSW, MPH; Nancee Blum, MSW
(*Arch Gen Psychiatry.* 1992;49:362-368)

Polysomnographic Characteristics of Young Manic Patients: Comparison With Unipolar Depressed Patients and Normal Control Subjects

James I. Hudson, MD; Joseph F. Lipinski, MD; Paul E. Keck, Jr, MD; Harlyn G. Aizley, MEd; Scott E. Lukas, PhD; Anthony J. Rothschild, MD; Christine M. Waternaux, PhD; David J. Kupfer, MD
(*Arch Gen Psychiatry.* 1992;49:378-383)

SPECIAL FEATURE

Radiological Case of the Month

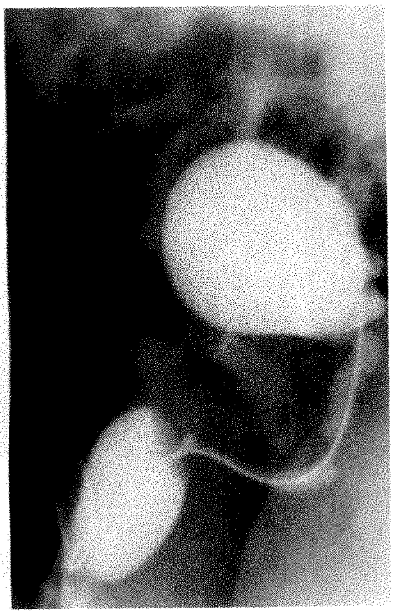
Edward E. C. Angtuaco, MD, Sarah G. Klein, ME (Contributors);
Beverly P. Wood, MD (Section Editor)

A 3½-month-old boy was referred to the hospital because of recurrent episodes of urinary tract infection. A voiding cystourethrogram was obtained to identify anatomic abnormalities.

Accepted for publication August 16, 1991.

From the Department of Radiology, Arkansas Childrens' Hospital, and the University of Arkansas for Medical Sciences, Little Rock.

Reprint requests to Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).



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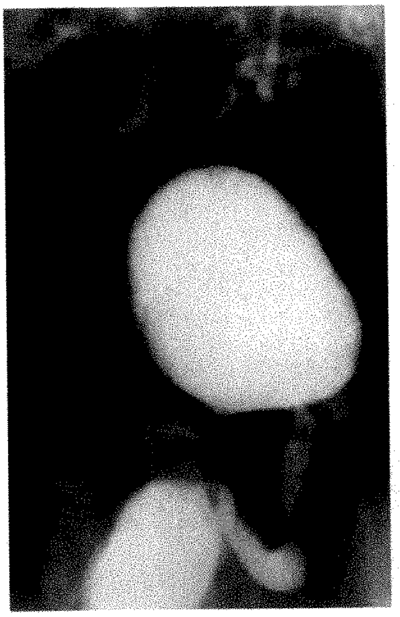

Figure 2.

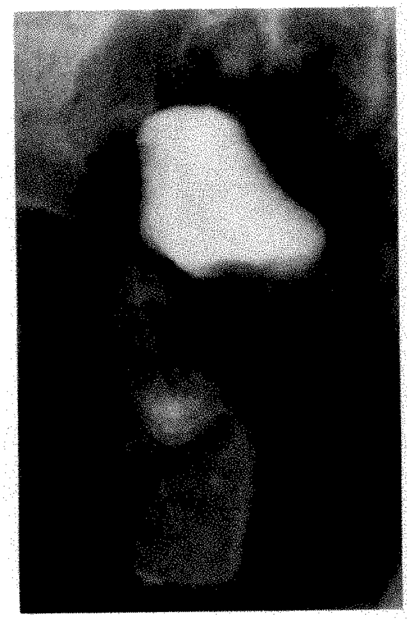

Figure 3.

Denouement and Discussion

Pathologic Phimosis

Fig 1.—*A voiding film with the urethral catheter still in place demonstrating an unusual appearing focal collection of voided contrast medium surrounding the tip of the urethra. The concave posterior margin of this collection of medium was persistent and represents the space between the prepuce and the glans penis. The catheter outlines the exact path of the urethra.*

Fig 2.—*Collection of contrast medium increased as voiding progressed. The remainder of the urethra, as well as the bladder, appeared normal. Mild, grade 1, vesicoureteral reflux is evident to the right.*

Fig 3.—*On completion of voiding, this collection of contrast medium slowly cleared as urine trickled out of the penis. A moderate amount of residual urine remained in the bladder.*

Pathologic phimosis occurs secondary to repeated tears in foreskin, which result in constricting, circumferential cicatrices.[1] Clinically, it presents as a nonretractable, thickened distal ring of foreskin. Treatment options include frequent cleansing, application of compresses, steroids, or antibiotic creams, foreskin dilatation using sounds or hemostats, and circumcision.

Differential diagnoses based on roentgenographic appearance of the affected area include urethral diverticulum, cystic anomalies of Cowper's glands and ducts, and megalourethra.

Phimosis is defined as a condition in which the prepuce is not fully retractable over the glans penis.[2] Physiologic and pathologic phimosis are distinct conditions. A study by Gairdner[3] and a later study by Oester[4] demonstrated that only 4% of newborns have fully retractable foreskin. However, this changes with growth. The foreskin of 20% of boys can be retracted by age 6 months; 50%, by age 1 year, 80%, by age 2 years; 90%, by age 3 years; and 99%, by age 17 years. Nonretractability is usually asymptomatic. Occasionally, as in this patient, there may be ballooning of the foreskin after voiding, causing postvoid dribbling and a characteristic appearance on voiding cystourethrograms.

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The Editors welcome contributions to Pathological Case of the Month, Picture of the Month, *and* Radiological Case of the Month. *Those who wish to contribute should send their manuscripts to Dr Gilbert-Barness (*Pathological Case of the Month*), Center for Health Sciences, E51326, University of Wisconsin Hospitals and Clinics, Madison, WI 53792; Dr Tunnessen (*Picture of the Month*), The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104; or Dr Wood (*Radiological Case of the Month*), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Radiological Case of the Month

Dennis R. Durbin, MD (Contributor), *Beverly P. Wood, MD* (Section Editor)

An 18-month-old, previously healthy boy presented to the emergency department with progressive lethargy and protracted emesis approximately 18 hours after ingestion of an unknown medication.

His mother had seen pills in his hands the previous night, but thinking the medication was harmless, did not seek medical attention. The child was asymptomatic at that time. He awoke 8 hours before admission with emesis and nonbloody diarrhea and became progressively lethargic. Pills and pill fragments were in his stool.

On physical examination, he was afebrile and had a pulse of 122 beats per minute. His respiratory rate was 32 breaths per minute. Blood pressure was 108/69 mm Hg. He was lethargic, but could be aroused, and had cool extremities. Examination of the abdomen revealed active bowel sounds and diffuse tenderness to palpation. Results of a test to detect occult blood in stool were negative. Except for changes in mental status, results of neurologic examination were unremarkable. Laboratory tests revealed the following values: sodium, 133 mmol/L; bicarbonate, 14 mmol/L; and glucose, 7.2 mmol/L. His hemoglobin level was 142 g/L, and his white blood cell count was 15.9×10^9/L. An abdominal roentgenogram was obtained (Figure).

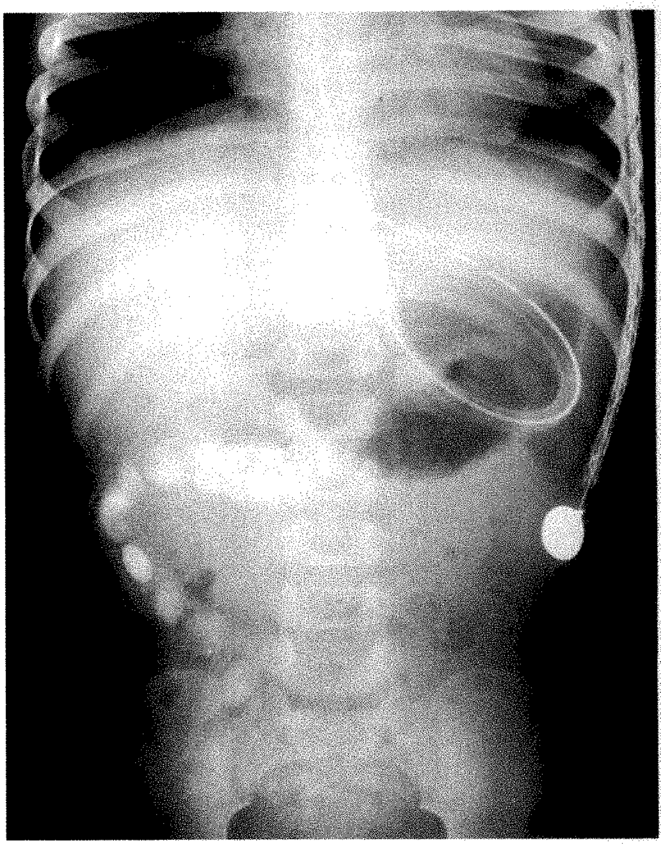

Figure.

Accepted for publication August 15, 1991.

Contributed from the Department of Pediatrics, Children's Hospital of Philadelphia (Pa).

Reprint requests to Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Denouement and Discussion

Acute Iron Poisoning and Gastrointestinal Decontamination Procedure

Figure.—*Frontal supine roentgenogram of the abdomen demonstrates crescentic arrangement of many ovoid, radiopaque, intraluminal densities in the right upper quadrant. These conform to a loop of colon or small bowel. A moderately distended, more proximal loop of small bowel is present. There is no obstruction or free air.*

The child had ingested approximately 30, 325-mg ferrous sulfate tablets (120 mg of elemental iron per kilogram). His serum iron level on admission was 63 μmol/L. Management included intravenous administration of fluids for hemodynamic stabilization, intravenous infusion of the specific chelator deferoxamine mesylate (10 mg/kg per hour), and continuous nasogastric infusion of polyethylene glycol electrolyte lavage solution (Golytely, Braintree Laboratories Inc, Braintree, Mass) for gastrointestinal decontamination.

The infusion of lavage solution was slowed and then stopped after 24 hours owing to persistent emesis, progressive abdominal distention, and pain to palpation. On the second hospital day, he began passing a liquid, black, blood-tinged, granular stool full of iron sediment. Follow-up abdominal roentgenograms showed dissolving radiopaque tablets progressing distally through the colon. The abdominal distention and tenderness resolved in the next 2 days.

Many parents do not appreciate the toxic potential of iron preparations. Ingestions of greater than 40 mg of elemental iron per kilogram are regarded as having potentially serious side effects.[1] The clinical course of iron toxicity has been divided into four phases.[2] Phase 1 occurs in the first 4 to 6 hours after a significant ingestion and consists of manifestations of the direct corrosive effects of iron on the gastrointestinal mucosa. Common signs and symptoms include emesis, diarrhea, hematemesis, melena, and abdominal pain. Phase 2 occurs 6 to 12 hours after an ingestion and consists of a relatively asymptomatic period during which free iron is distributed to various organs and peripheral tissues. Patients may exhibit intermittent lethargy. Phase 3 occurs 12 to 48 hours after an ingestion and can be marked by shock, lethargy, coma, metabolic acidosis, further gastrointestinal hemorrhage, hepatic dysfunction, and coagulopathy. Free, unbound iron in the circulation and peripheral tissues is responsible for most of these symptoms. A relatively rare complication of severe iron toxicity, Phase 4, may occur 4 to 6 weeks after an ingestion and consists of gastrointestinal scarring with stricture formation and bowel obstruction at the site of a previous mucosal injury.

The standard management of significant iron poisoning has been the use of deferoxamine in addition to various methods of gastrointestinal decontamination.[3] Because activated charcoal does not adsorb iron,[4] and the efficacy of ipecac-induced emesis and gastric lavage have been questioned,[5,6] whole-bowel irrigation with a polyethylene glycol electrolyte lavage solution has emerged as a safe, effective means to prevent absorption of iron from the gastrointestinal tract.[7]

Total-bowel irrigation is the technique of administering large volumes of a balanced electrolyte solution, either orally or via a nasogastric tube, to produce diarrhea when the infusion rate of the fluid exceeds the capacity of the bowel to distend and retain the solution.[8] Indications proposed for the use of this treatment include poisoning by ingestion of delayed-release pharmaceuticals, poisoning by iron or other agents not adsorbed by activated charcoal, and a late presentation after ingestion of a toxin.[7]

Because iron has a well-known, direct corrosive effect on the gastrointestinal mucosa,[1,3] late presentation after an acute iron ingestion may lead to significant gastrointestinal damage. Caution is advised with use of whole-bowel irrigation in a patient who may have sustained mucosal injury. Patients, including children, with damaged mucosal membranes secondary to chronic inflammatory bowel disease have tolerated bowel preparation using polyethylene glycol electrolyte lavage solution without untoward effects.[9,10] However, major gastrointestinal dysfunction, including ileus, bowel obstruction, perforation, or significant gastrointestinal hemorrhage, are contraindications to whole-bowel irrigation.[7]

The polyethylene glycol electrolyte lavage solution, is administered either orally or via a nasogastric tube at a rate of 0.5 L/h for children age 5 years or younger and at a rate of 2 L/h for adolescents and adults.[11] The procedure is continued until the rectal effluent resembles the infusate (which generally takes 6 to 12 hours).[11] Side effects are nausea, vomiting, abdominal cramps and fullness. [8,10]

The successful use of whole-bowel irrigation in the treatment of acute iron poisoning has been recently described[11-13] and is a safe, effective means of gastrointestinal decontamination for iron poisoning

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SPECIAL FEATURE

Picture of the Month

A. Engin Arisoy, MD; Serap Ozden, MD; E. Sami Arisoy, MD; Kenan Kocabay, MD;
Huseyin Guvenc, MD (Contributors)*; Walter W. Tunnessen, Jr, MD* (Section Editor)

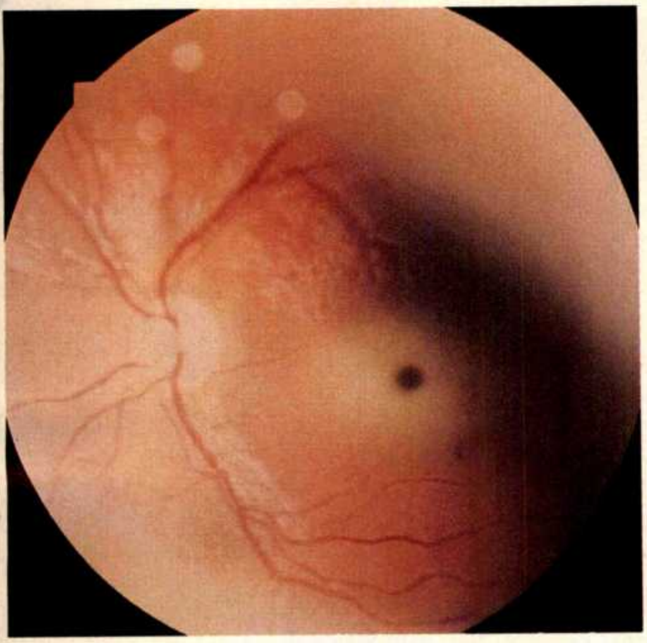

Figure 1.

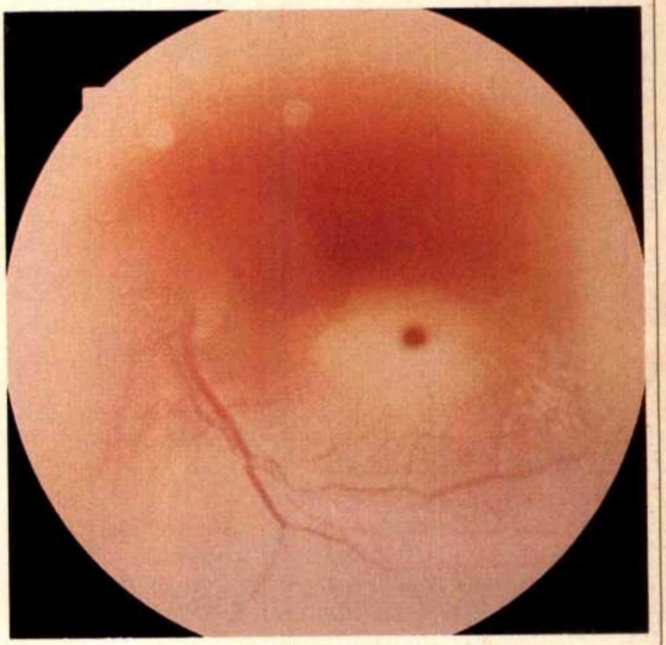

Figure 2.

Retinal changes in an apathetic infant with progressive mental and physical retardation.

Accepted for publication August 24, 1991.

Contributed from the Departments of Pediatrics (Drs A. E. Arisoy, E. S. Arisoy, Kocabay, and Guvenc) and Ophthalmology (Dr Ozden), Firat University School of Medicine, Elazig, Turkey.

Reprint requests to The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Tunnessen).

Denouement and Discussion

Tay-Sachs Disease

Figs 1 and 2.—*A classic cherry-red spot is visualized in the macula of both eyes.*

Manifestations

The characteristic cherry-red spots of Tay-Sachs disease were first described in 1881 by Warren Tay, a British ophthalmologist, in a 1-year-old child with mental and physical retardation.[1] Bernhard Sachs, a neurologist, coined the term familial amaurotic idiocy for this disorder and described the typical morphologic feature of the disease: distended cytoplasm of the neurons and ballooning of their dendrites. In the 1930s, Ernst Klenk, a biochemist, used the name *gangliosides* to describe the glycolipid accumulation in ganglion cells characteristic of this disease.[1]

Tay-Sachs Disease, now referred to as GM_2 gangliosidosis, type 1, has a classic progression. Affected infants appear normal at birth. The earliest signs, beginning at age 3 to 5 months, are mild motor weakness and myoclonic jerks associated with sharp noises. Most often, these signs are not recognized by the parents, except in retrospect. Between ages 6 and 10 months, there is a progressive loss of motor function with weakness, hypotonia, poor head control, and decreased attentiveness to surroundings. The exaggerated response to auditory stimuli suggests hyperacusis. Visual signs, such as unusual eye movements and episodes of staring, or concerns about decreased visual acuity, may lead to ophthalmologic consultation, the discovery of the cherry-red spots (Figs 1 and 2), and ultimately the diagnosis of GM_2 gangliosidosis.

After age 1 year, the central nervous system steadily degenerates. Seizures may become prominent; spasticity with hyperactive reflexes, blindness, and deafness follow. The face takes on a doll-like expression, with translucent skin and long eyelashes. Macrocephaly secondary to cerebral gliosis becomes apparent by age 18 to 24 months. Intercurrent respiratory infections are common, and death usually occurs between ages 2 and 4 years.

The most characteristic feature of Tay-Sachs disease is the cherry-red spot of the macula. This finding actually represents a normal red macular area surrounded by a white area, the result of lipid accumulation in the retinal ganglion cells. The spot later becomes darker and brownish as the macula degenerates, and opaque whitish streaks along vessels may be observed. Cherry-red spots may be noted as early as age 3 months.

The cherry-red spots are not pathognomonic for Tay-Sachs disease. They can be seen in retinal ischemia and contusion of the globe, generalized gangliosidosis, Sandhoff disease, metachromatic leukodystrophy, Niemann-Pick disease, Farber disease, and sialidosis (types 1 and 2).[2] However, the discovery of a cherry-red spot in a Jewish infant, a typical clinical course, and the absence of organomegaly are strongly suggestive of Tay-Sachs disease.

Diagnosis

The basic defect in this disorder is a deficiency of hexosaminidase A, which is responsible for hydrolyzing GM_2 ganglioside, the glycolipid that accumulates in neurons. The deficency of hexosaminidase A can be demonstrated in serum, plasma, leukocytes, and cultured fibroblasts of affected infants. A simple and inexpensive measurement of this enzyme has enabled population screening for heterozygotes in Jewish communities. A newer DNA-based test with increased specificity and predictive value has proven useful when used as an adjunct to screen carriers for this disorder.[3] Prenatal diagnosis can be accomplished by measuring this enzyme in amniotic fluid, cultured amniocytes, or chorionic villus samples.

Genetics

Tay-Sachs disease has an autosomal-recessive mode of inheritance. The two abnormal alleles of the hexosaminidase α locus on chromosome 15 account for almost all infantile cases in Ashkenazi Jews. The severity of the disease appears to correlate with the level of residual enzyme activity. An abnormal carrier state affects approximately one in 31 individuals of Ashkenazi Jewish ancestry, but only one in 167 individuals in the non-Jewish population.[1]

Treatment

No specific therapy for the treatment of Tay-Sachs disease is available. Supportive care includes management of hydration, intercurrent infections, and seizures.

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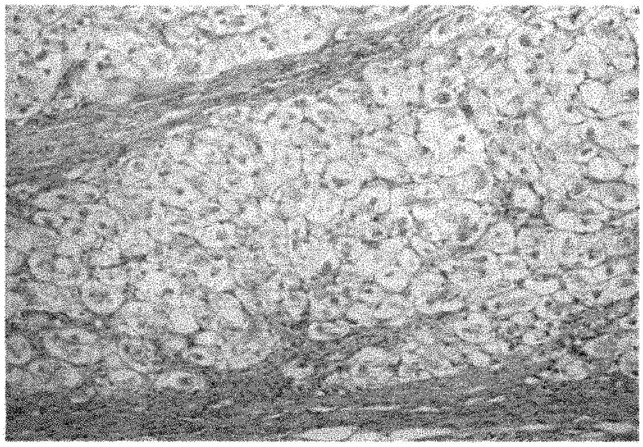
SPECIAL FEATURE

Pathological Case of the Month

Lewis Barness, MD (Contributor), *and Enid Gilbert-Barness, MD* (Contributor and Section Editor)

A 4-year-old girl presented with the chief complaint of jaundice and failure to thrive. At birth, she weighed 1.7 kg. Neonatal jaundice and ascites were present, but resolved in 2 weeks. She was discharged from the hospital at age 5 weeks weighing 2.1 kg. She gained weight poorly and was readmitted at age 4 months. She was jaundiced. Laboratory values in serum were as follows: total bilirubin, 110 µmol/L (80% direct); alanine aminotransferase, 240 U/L; aspartate aminotransferase, 75 U/L; and ammonia, 160 µmol/L. Levels of urine and serum amino acids were also determined. She started on a low-protein diet and was discharged from the hospital.

She was unavailable for follow-up until presentation. At that time, her serum bilirubin level was 444 µmol/L. Two weeks after admission, she developed acute gastrointestinal bleeding. Laboratory values were as follows: platelet count, 35×10^9/L; serum ammonia, 125 µmol/L; alkaline phosphatase, 17.9 U/L; bilirubin, 270 µmol/L; white blood cell count, 15.7×10^6/L; prothrombin time, 12.1/21.4 seconds; albumin, 19 g/L; and glucose, 2.0 mmol/L. She was treated with intra-arterial vasopressin, norepinephrine bitartrate, and blood transfusions. Roentgenograms were suggestive of portal hypertension, splenomegaly, and possible gastric and esophageal varices. A liver biopsy was performed (Figs 1 and 2), and she subsequently underwent liver transplantation. The pathologic features of the resected liver are shown in Figs 3 and 4.



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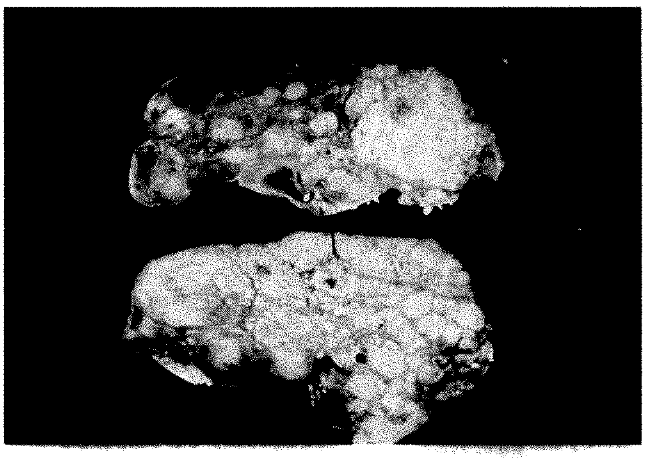

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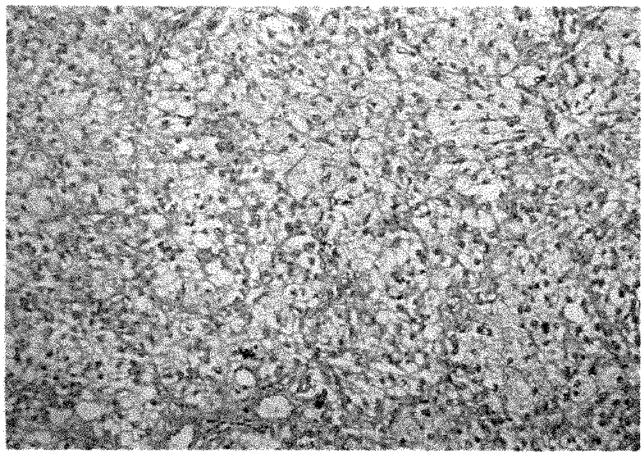

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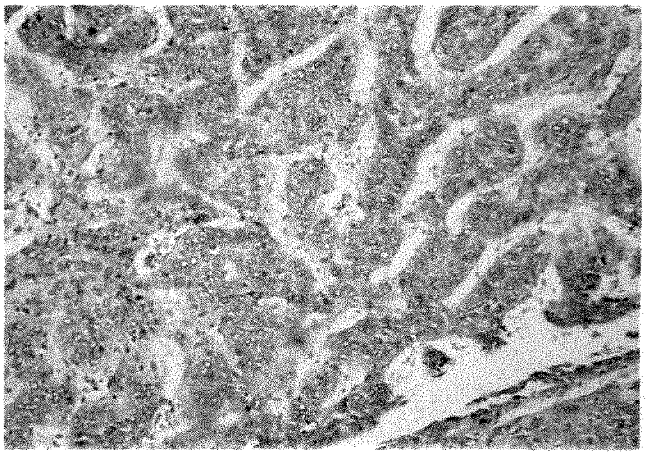

Figure 4.

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Contributed from the Departments of Pathology and Pediatrics, University of Wisconsin, Center for Health Sciences, Madison.
Reprint requests to Departments of Pathology and Pediatrics, University of Wisconsin, Center for Health Sciences, E5/326, 600 Highland Ave, Madison, WI 53792.

Diagnosis and Discussion

Hereditary Tyrosinemia Type I

Fig 1.—*Microscopic appearance of the liver on biopsy showing cirrhosis and regenerative nodule (hematoxylin-eosin, original magnification ×100).*

Fig 2.—*Microscopic appearance of the liver on biopsy showing fatty change of hepatocytes (hematoxylin-eosin, original magnification ×250).*

Fig 3.—*Gross appearance of resected liver showing macronodular cirrhosis and nodules of tumor.*

Fig 4.—*Microscopic appearance of tumorous nodule showing trabecular pattern of hepatocellular carcinoma.*

Hereditary tyrosinemia type I is an autosomal recessive disorder characterized by elevated levels of tyrosine and its metabolites. It results from a deficiency of fumarylacetoacetase, a critical enzyme in the catabolism of tyrosine; the outcome is an accumulation of abnormal metabolites.[1] The condition may be acute or chronic. The acute form occurs in early infancy and results in failure to thrive, vomiting, diarrhea, a cabbagelike odor, hepatomegaly, and death owing to liver failure at age 6 to 8 months.[1,2] In the chronic form of the disease, chronic liver disease develops by age 1 year together with renal tubular dysfunction and porphyrialike symptoms. Hepatocellular carcinoma is a common complication that occurs later in childhood in 39% of cases.[3]

This patient manifested most of the characteristics of the chronic form of tyrosinemia type I, including renal tubular dysfunction, growth retardation, deranged coagulation, hypoglycemia, cirrhosis, and elevated levels of serum bilirubin and hepatic enzymes. Analysis of urinary amino acids showed elevated tyrosine levels of 1060 mmol per gram of creatinine (normal value, 0.33±0.23 mmol per gram of creatinine) and elevated methionine levels of 1453 mmol per gram of creatinine (normal value, 0.28±0.23 mmol per gram of creatinine). Because the primary defect in this syndrome is deficiency of fumarylacetoacetase,[4] the last enzyme involved in the degradation of tyrosine, maleylacetoacetase and fumarylacetoacetase, intermediates in tyrosine catabolism, accumulate. These intermediates are natural alkylating agents[1,5] with all the characteristics to make them primary candidates for carcinogenesis.[5] They are also presumed to directly cause other cellular damage associated with the syndrome. Maleylacetoacetase and fumarylacetoacetase cannot be measured directly, but their levels are reflected in the accretion of succinylacetone, the form in which they are excreted.[4,6]

Elevated levels of methionine and tyrosine in serum, generalized aminoaciduria, and large increases in tyrosine metabolites (4-hydroxyphenyllactic and 4-hydroxyphenylpyruvic acids) in urine[7,8] may develop in metabolic disorders associated with hepatocellular disease, such as hereditary tyrosinemia, galactosemia, hereditary fructose intolerance, fructose-1,6-diphosphatase deficiency, glycogenosis type IV (amylopectinosis), and α_1-antitrypsin deficiency.

Pathologically, the liver is typically enlarged, yellow, firm, and nodular.[9] Microscopic changes include formation of multiacinar areas of fibrosis alternating with nodules of regeneration or preserved parenchyma that shows striking fatty metamorphosis, cholestasis, and pseudogland transformation. These changes are similar to those present in galactosemia and hereditary fructose intolerence. Hepatocellular carcinoma is frequent in patients with tyrosinemia who survive beyond age 2 years.[10] Liver transplantation can cure tyrosinemia and hepatocellular carcinoma.[11]

Chromosomal instability, with increased chromosome breakage in hereditary tyrosinemia type I, has been demonstrated in cultured skin fibroblasts.[12] This suggests that the development of hepatoma is related to genetic instability caused by accumulation of intermediates of tyrosine catabolism.

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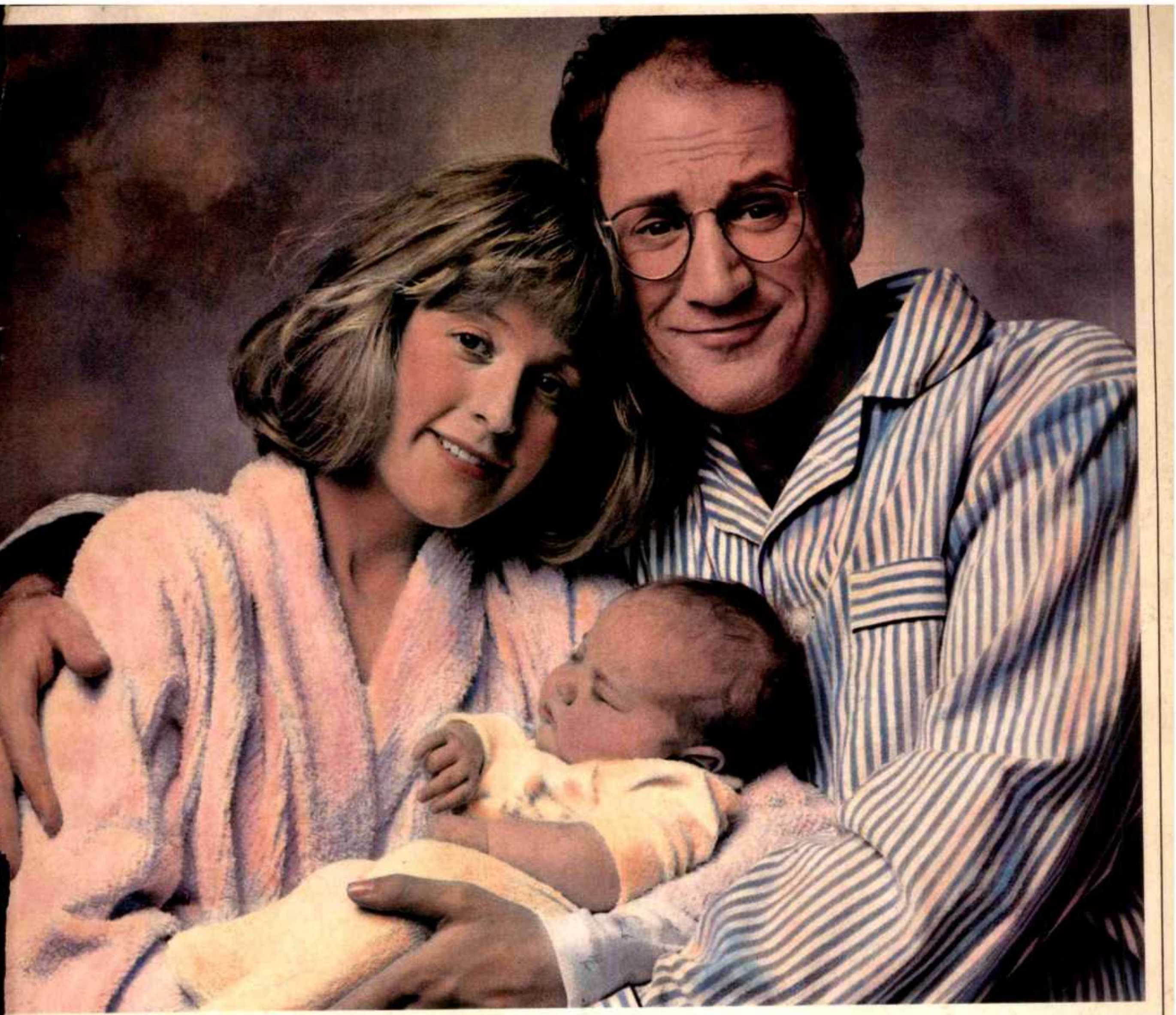

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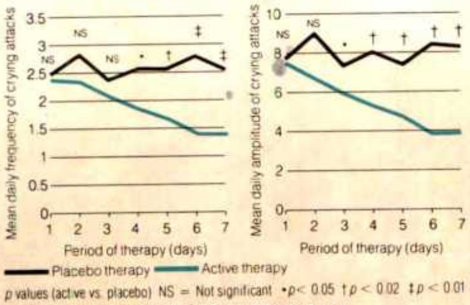

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